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ANALYSIS AND STANDARDIZATION OF HOUSE DUST BY GEL DIFFUSION

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A REVIEW of the literature indicates that there is no doubt that house dust is an extremely potent allergen, and is the cause of more human allergy than any other single allergen with the possible exception of ragweed pollen. But, as to the nature of its antigen or antigens, scarcely any two allergists agree. E. A. Brown in his two comprehensive reviews of the literature on dust allergy,[3,4] which are so all-inclusive as to make any further review superfluous, summarizes the situation as follows: "Evidence has been presented that the dust antigen is due to molds alone, to degenerated cotton linters alone, and to the effects of molds and bacteria upon linters, kapok and other substances." Evidence has also been presented "that the antigen is in part epithelial scales, bacteria, and rodent and insect feces.—We do not know whether we are dealing with one or a number of similar antigens, or whether what we are using is derived from degenerated vegetable fibre, or such fibres acted upon by molds or bacteria. Remembering, as noted above, that a number of other substances may be present and play a part in the complex of house dust sensitivity, these may actually be a part of the material with which we are working."

Further light is thrown on this perplexing subject by Rimington and Maunsell,[11] who find that the dust antigens are a combination of a polysaccharide (hexose) and polypeptides. The carbohydrates can be removed by hydrolysis without destruction of the antigen. Electrophoresis experiments show that there are two antigens or else one antigen occluded on two substances of different mobilities in the electric field.

Rimington[10] concludes that "although house dust—might be expected

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to contain a great variety of allergens, experience has shown that sensitivity to house dust is rather highly specific. One hypothesis—is that the allergenic material—is the product of the action of microorganisms upon vegetable fibres and is not found in either of these materials separately."

Maunsell[5] finds that there is more house dust allergy in damp places and that this higher incidence follows the course of buried rivers in the London area. Allergy to house dust is not assumed to be due to fungi. "A hypothesis, however, is set forth that the house dust allergen may be produced in greater quantity per unit of dust by the action of fungi. There may be produced, from different sources, a uniform house dust antigen, with its own specificity in morphological appearance, chemical nature and immunological behavior."

It seems to the present writer that little more can be learned about the house dust allergen by the old approaches, and that all attempts at its standardization are futile without a knowledge of its antigenic structure.

A new approach to both these problems is offered by the technique of serum-agar diffusion recently developed by Oudin,[9] Ouchterlony,[8] Björklund,[2] Oakley,[7] Munoz[1,6] and others. Their methods have been shown to be fully applicable to the antigenic analysis and standardization of pollen extracts.[13] The present investigation, though only of a preliminary nature, shows that they are equally applicable to the allergen of house dust, and can answer some of the problems posed above.

MATERIALS AND METHODS

Dust Allergens.—No. 1 extract was prepared from upholstery dust collected locally in February, 1951.

No. 2, prepared from material similar to No. 1, was collected in March, 1949.

No. 3, prepared from upholstery dust, was collected at stations outside the local area, nation wide, April, 1949.

No. 4, prepared from carpet dust, was supplied by Reliable Rug Cleaning Company, Paterson, New Jersey.

No. 5, origin unknown, was prepared in 1927.

No. 6 is a commercial extract said to be prepared from mattresses and household furniture about 1946.

No. 7, a newer preparation of No. 6, was prepared about 1951.

Rabbit Antisera.—Nos. P 21 to P 30 are pools of sera prepared from dust No. 1.

P 21 combines the first bleedings from three rabbits.

P 22 is P 21+second bleedings from the same rabbits.

P 30 is P 22+third bleedings from the same three rabbits+the first bleeding from a fourth.

P 31 is the pooled serum of the first bleedings from two rabbits treated with carpet dust No. 5.

Human Dust-sensitive Sera.—Del G serum from a patient suffering from asthma from house dust and exposure to laboratory animals. He was shown to be highly sensitive to house dust by direct test and passive transfer. He was also sensitive to a lesser degree to rabbit dander but this failed to transfer.

Gr serum.—From a patient highly sensitive to house dust (confirmed by passive transfer) also mildly sensitive to cat and slightly to rabbit danders and feathers by direct test, but these failed to transfer.

Jo serum. Highly sensitive to house dust (confirmed by passive transfer) also moderately sensitive by direct test to feathers and rabbit dander but these latter failed to transfer.

Preparation of Diffusion Plates.—Plain agar, 1 per cent in buffered saline+1:5000 merthiolate was melted and poured in a thin layer on to glass plates 3¼ x 4 inches. After jellying in the refrigerator three penicillin cups were placed on the surface of each plate in a triangular configuration, 20 mm apart rim-to-rim. Into these were poured the reactants to be tested. As the materials diffused into the agar, the cups were refilled twice, usually at intervals of three or four days.

As the diffusion areas from allergenic extracts encroach upon those from their corresponding antisera zones of equivalence are established between their various antigens and their homologous antibodies resulting in precipitation bands. For comparison of allergenic extracts with each other, it is most instructive to place two of the allergens into two cups of a group of three and the homologous antiserum of one or the other or both in the third. Bands from the two antigen sources which form continuous arches about the serum cup indicate identity of antigens, those which cross without interference indicate nonidentity.

In the same way two antisera may be compared by allowing them to diffuse against the same allergen (Fig. 1). The bands are generally arched and presenting their concave side to the source of the proximal reactant. With serum P 30, its homologous serum, dust No. 1 gives three precipitation bands which, for convenience, have been designated *a*, *b*, *c*, lettered in order of their distance from the antigen cup. This is the characteristic pattern for dust No. 1. Band *a* is the weakest, faint and not sharply defined but with a tendency to split as if actually consisting of two bands more or less superimposed. Bands *b* and *c* are sharply defined and with no apparent tendency to split, but band *c* is much the heavier of the two. With serum P 31, with which it is heterologous, dust No. 1 gives only two bands which are easily identified with bands *b* and *c*, since they form continuous arches. although band *a* is absent in the P 31 field, it should be noted that the proximal end of this band is bent as it encroaches upon the P 31 field, indicating that, although there is insufficient antibody in P 31 to form a

precipitation band of its own, there is enough to interfere with that from P 30. It is thus apparent that P 31, though made from an entirely different dust preparation, No. 4, has the same three antibodies, but in different proportions. Also P 31 is weaker in antibody, since it establishes zones of equivalence more remote from the antigen source than P 30.

The following comparisons of the house dust extracts were made to discover the presence or absence of common antigens in those from the same and different sources.

Dust No. 1 compared with Dust No. 2 diffusing against serum P 22 which is homologous with dust No. 1 (Fig. 2). The right hand side of the arch shows the characteristic pattern of precipitation bands of dust No. 1 very much as seen in Figure 1. Moreover, they all interfere with each other forming a nearly symmetrical arch, only slightly distorted in favor of dust No. 2 showing that No. 2 is stronger in antigen. As before, band *c* is much the heavier of the three and more sharply defined. Therefore, it seems justifiable to describe this dust preparation as having one major and several minor antigens, which has proved to be the case with most allergens so far examined. Since these three bands are duplicated on the other side of the arch, the two extracts are identical insofar as these antigens are concerned, which is more or less to be expected since they were prepared from materials from the same source though collected at different times.

Dust No. 1 compared with No. 3 (Fig. 3) shows that two of the antigens are identical, but the one corresponding to band *b* is much weaker in No. 3, enough to turn the *b* band though not enough to form an independent precipitate.

Dust No. 1 compared with No. 4 (Figs. 4, 5, 6). In this case antisera for both extracts were available. They were seen diffusing against dust No. 1 in Fig. 1. The two extracts are shown diffusing against serum P 30 (Fig. 4). Dust No. 1, on the left, shows its usual pattern but the antigen of band *b* is only weakly represented in dust No. 4. When diffused against P 31 which is homologous with No. 4 only two bands are formed and these only weakly with No. 4 (Fig. 5), obviously due to the low titer of serum P 31. When diffused against the combined sera (Fig. 6), dust No. 1 produces its normal three banded pattern, but one of its

EXPLANATION OF FIGURES

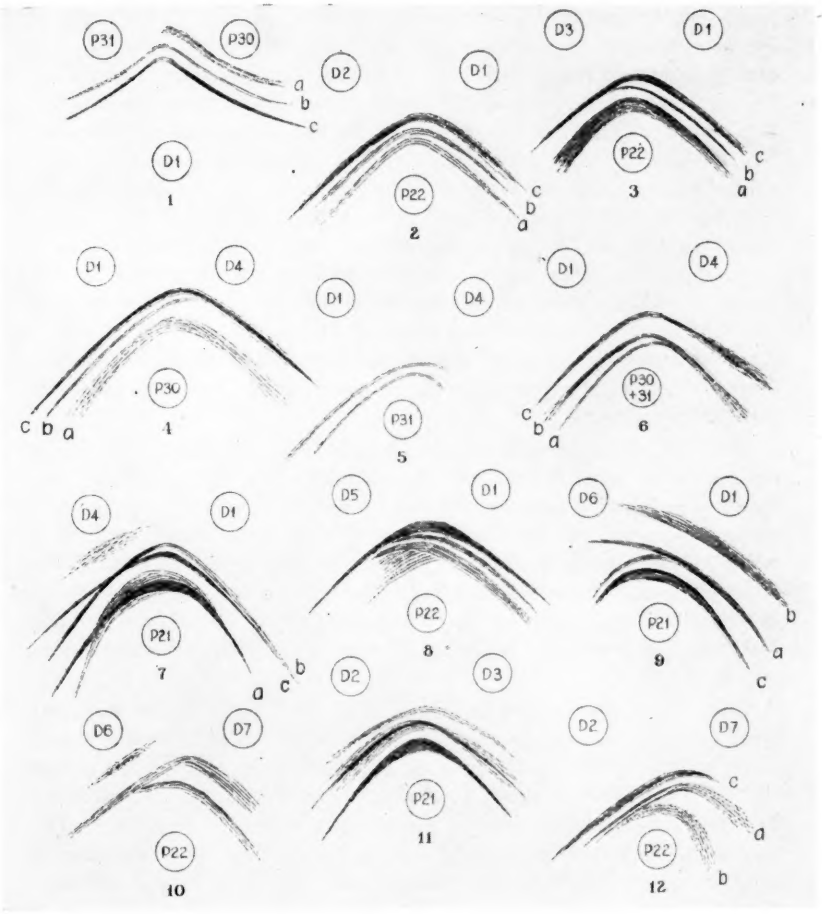
Reproduced at 0.775 actual size. In all cases except where otherwise stated the antisera were used undiluted.

Fig. 1. Antidust sera, P 31 and 30 (made by dust extracts No. 4 and 1), diffusing against dust No. 1, 20 M u/ml., appearance after eight days.

Fig. 2. Dust extracts No. 2 and 1, 20 M u/ml each diffusing against antiserum P 22, homologous with No. 1, appearance after nine days.

Fig. 3. Dust extracts No. 3 and 1, 20 M u/ml each diffusing against antiserum P 22, appearance after nine days.

Fig. 4. Dust No. 1 compared with No. 4, 20 M u/ml each diffusing against serum P 30, homologous with dust No. 1, appearance after nine days.



Figs. 1-12.

Fig. 5. As in the preceding figure, but diffusing against antiserum P 31, homologous with dust No. 4, appearance after nine days.

Fig. 6. As in the two preceding figures but the antigens diffusing against the two antisera combined in equal parts, appearance after nine days.

Fig. 7. Dust No. 4, 181 M u/ml compared with No. 1, 190 M u/ml, diffusing against antiserum P 21, appearance after twelve days.

Fig. 8. Dust No. 5 and No. 1, each 20 M u/ml compared diffusing against antiserum P 22, appearance after nine days.

Fig. 9. Dust No. 6 and No. 1, 20 M u/ml, diffusing against serum P 21, homologous with No. 1, appearance after sixteen days.

Fig. 10. Dust 6 and No. 7, 400 M u/ml compared diffusing against P 22 to which both are heterologous, after nine days.

Fig. 11. Dust No. 2 and No. 3, 20 M u/ml each diffusing against serum P 21 with which both are heterologous, after twelve days.

Fig. 12. Dust No. 2, 20 M u/ml compared with No. 7, 400 M u/ml compared, diffusing against serum P 22, after nine days.

two bands is bent by No. 4, showing that this extract carries some of the same antigen. The presence of all three antigens in dust No. 4 is brought out when the concentration of the antigens is increased (Fig. 7). In this, dust No. 1 shows its usual three precipitation bands, but apparently, the major antigen is now in the middle position. On the dust No. 4 side of the arch, it crosses over to its more usual position. On this side of the arch the composite nature of the *a* band is brought out, also No. 4 shows a fourth precipitate close to the antigen cup. Thus, it is seen that dust No. 4 has all the antigens that were found in No. 1, together with another which was not found, probably because it was below the concentration of equivalence. Its presence is implied in dust No. 1 because of its antibody in serum P 21, which was produced by it. This experiment demonstrates that the same dust antigens can be obtained from materials of widely different origins, though they may occur in different proportions.

Dust No. 1 compared with dust No. 5 (Fig. 8). That the major antigen is the same in both these preparations, is indicated by the continuous precipitation arch, but the *a* and *b* antigens of dust No. 1 are only weekly represented in dust No. 5. However, this latter carries an antigen which is only slightly represented in dust No. 1, possibly the same as the antigen responsible for the extra band found in No. 4, as suggested by its broad and diffuse structure. In this case the precipitate is formed much closer to the serum cup, showing its relatively higher concentration in No. 5.

Dust No. 1 compared with No. 6 (Fig. 9). No. 1 shows its usual three precipitation bands, but in this case the major band is formed closest to the serum cup. This and part of the *a* band are fairly represented in dust No. 6. The split in *a* shows conclusively that it is double and mediated by two different antigens, one of which is not present in dust No. 6. The advanced position of the major or *c* band appears to be due to the additive effect of its antigens from the two sources. But the *b* antigen is absent from No. 6.

Of course, it is quite possible that dust No. 6 has antigens for which it finds no antibodies in serum P 21, since this is heterologous to it. This question can only be answered when a precipitating serum for this extract can be prepared. Attempts to do this have so far failed.

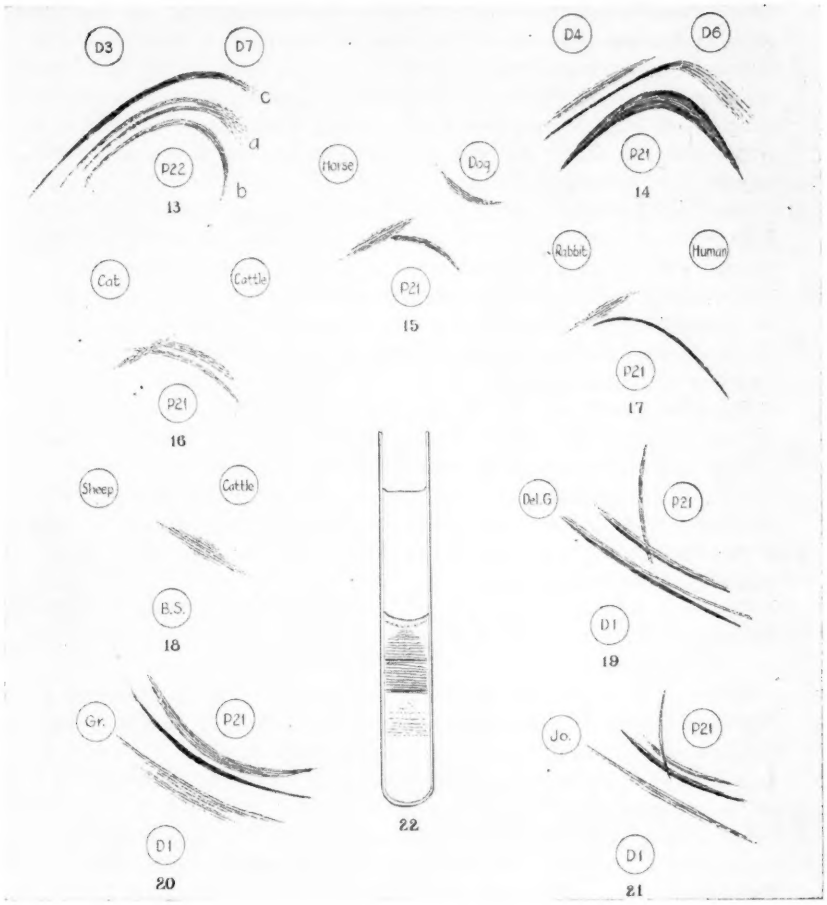
Dust No. 6 compared with No. 7 (Fig. 10). Since these are diffused

EXPLANATION OF FIGURES

Reproduced at 0.775 actual size. In all cases except where otherwise stated the antisera were used undiluted.

Fig. 13. Dust No. 3, 20 M u/ml and No. 7, 400 M u/ml, diffusing against serum P 22, after nine days, cf fig. 12.

Fig. 14. Dust No. 4, 181 M u/ml and No. 6, 400 M u/ml diffusing against serum P 21, after seven days.



Figs. 13-22.

Fig. 15. Horse and dog dander extracts, both 20 M u/ml diffusing against serum P 21, after fifteen days.

Fig. 16. Cat and cattle dander extracts, each 20 M u/ml diffusing against antidust serum P 21, after fifteen days.

Fig. 17. Rabbit dander, 20 M u/ml and normal human serum undiluted, diffusing against antidust rabbit serum P 21, after fifteen days.

Fig. 18. Sheep and cattle danders, 60 M u/ml diffusing against human bovine sensitive serum (B.S.) concentrated three times, appearance after eighteen days.

Fig. 19. Dust extract No. 1, 20 M u/ml diffusing against antidust serum P 21 compared with Del G human dust sensitive serum, appearance after eighteen days.

Fig. 20. As above but compared with Gr human dust sensitive serum, after twenty-one days.

Fig. 21. As above but compared with Jo human dust-sensitive serum, after twenty-one days.

Fig. 22. Dust extract No. 1 50 M u/ml diffusing into antidust serum P 30+ .6% agar, in equal parts, appearance after ninety-six hours.

against an antiserum which is heterologous for both of them, this must be considered a somewhat incomplete picture. However, it does show that they both have antigens that are common to dust No. 1 for which the antiserum is homologous. One band which appears to be from the major antigen and one of the minor antigen bands are common to both dust preparations but widely different in proportion, while a third one in No. 6 appears to be lacking in No. 7.

Dust No. 2 compared with No. 3, diffusing against serum P 21 (Fig. 11). The precipitation bands of both completely interfere, forming symmetrical arches showing identity of antigens insofar as revealed by this antiserum which was heterologous with both, since it was prepared from dust No. 1. However, it has already been shown that No. 2 is essentially the same as No. 1. Consequently, all three extracts may be regarded as nearly identical.

The behavior of dusts No. 2 and No. 3 with No. 7 are shown in Figs. 12 and 13. Dust No. 7 forms three bands which are identical with those of Nos. 2 and 3 except that the second band is split under the influence of No. 7. This identifies it with *a*. It has changed places with *b*. The synergistic effect of Dust No. 7 on *a* acts only enough on one of its parts to separate them a little, but its effect on *b* is enough to push it ahead of *a* toward the antibody source.

The extreme lopsidedness of the arch in both cases shows a faulty adjustment of dust No. 7. It should have been used at several times its present concentration.

Dust No. 4 compared with No. 6 at high concentration is shown in Fig. 14. Only the antigens are represented which find corresponding antibodies in serum P 21, which is homologous with dust No. 1. However, two of these, including the major, are common to both, while the third of No. 4 appears to be absent from No. 6.

It has long been suspected that even if house dust has an antigenic complex of its own, it also contains antigens of many specific inhalants. Experiments were done to throw some light on this question. When horse dander and dog dander were diffused against anti-house dust serum P 21 (Fig. 15), the horse dander gave one precipitating band and the dog two, widely separated and one of them apparently crossing the band from horse dander without intereference. All were extremely faint.

When cat dander and cattle dander were diffused against serum P 21 (Fig. 16), cat gave one precipitation band and cattle dander two, one of which crossed the band from cat without interference. All three were also extremely weak. When rabbit dander and human serum were diffused against antiserum P 21, both gave precipitating bands, the rabbit extremely faint but the human strong and sharp (Fig. 17). The fact that rabbit dander precipitates with rabbit antiserum suggests that the antigen involved was probably due to a contaminant not of rabbit origin and which is common to house dust. This casts suspicion on the specificity of the other

reactions except that of human serum. However, these precipitates differ from each other and are not due to a common contaminant because those from dog dander cross those from horse, and those from cattle dander cross those from cat dander without interference. On the other hand, the rabbit dander does turn the proximal end of the human band showing the presence of a common or similar substance in the two.

It has been shown that the serum of a patient sensitive to horse dander will give precipitation bands in agar with horse dander (12). In these studies the serum (B.S.) of a patient extremely sensitive to cattle, dog, goat and sheep danders, confirmed by passive transfer, gave a precipitation band with cattle dander (Fig. 18), though failing with the others.

Consequently, it seemed worth while to examine the three human anti-dust sera described above for house dust precipitating antibodies. When tested against dusts No. 1 and 6 all were negative. Two of these sera, Del G. and Jo, however, gave marked precipitating bands with rabbit antidust serum (Figs. 19, 21), though the third did not (Fig. 20).

All three of these human sera were from patients slightly to moderately sensitive to rabbit dander, but none showed transferable reagin, so it is not to be expected that these sera would carry precipitating antibodies against rabbit serum. The precipitation bands are in all probability merely a repetition of that shown in Fig. 17 with normal human serum acting as antigen.

STANDARDIZATION

The standardization of dust poses a more difficult problem than that of the pollens. With the latter, while different batches may vary widely in total activity, their antigenic structure is not likely to deviate widely from a mean unless the material is grossly mishandled in collection or preparation. Moreover, this can easily be put to the test by comparing the precipitation patterns of their extracts with that of the standard. After it is once established that the pattern of an unknown extract is the same as that of the standard, it may be standardized upon any one of its antigens, preferably the major since it gives the sharpest band and is easiest to read.

House dust, on the other hand, is very apt to vary more widely, not only in its total activity, but also in its antigenic patterns, according to the source of the raw material. However, if it is collected from the same or even similar sources, the antigenic patterns can be duplicated almost exactly as seen in dusts 1, 2 and 3. It is therefore, only necessary to select a good dust preparation having all the desirable therapeutic attributes, and of which the origin is accurately known, and set this up as the type standard. Such has been done with dust No. 1. Its antigenic pattern is known and it has been almost exactly duplicated. Its homologous antiserum has been prepared as Pool 30. When lyophilized this serum can be kept as a permanent standard of reference. Its graph for house dust No. 1 was prepared as follows.

TABLE I. ANTIGEN DILUTIONS OF STANDARD DUST EXTRACT

M Units Per ml	43 Hours				96 Hours			
	Band 1		Band 2		Band 1		Band 2	
	D	P	D	P	D	P	D	P
1.25	2.0	.305	—	—	2.65	.271	—	—
2.5	3.85	.587	1.8	.275	5.6	.572	2.35	.240
5.0	5.65	.812	3.0	.457	7.75	.792	4.1	.418
10.0	7.1	1.08	3.95	.602	9.75	.995	5.65	.577
20.0	7.7	1.17	4.95	.755	11.1	1.13	7.35	.770
40.0	8.7	1.33	5.9	.900	12.85	1.31	9.0	.920
80.0	10.2	1.55	7.35	1.12	14.9	1.52	10.5	1.07
100.0	11.15	1.70	7.9	1.20	15.25	1.57	11.3	1.15

D—distance of penetration.
P—penetration rate. Readings at 43 and 96 hours.

Serum of Pool 30 was diluted 1:6 with saline and combined with an equal volume of 0.6 per cent melted agar at 50° C., both preserved with 1:5000 merthiolate. Into each of sixteen Oudin tubes was poured 0.7 ml of the serum-agar, and allowed to jell in the refrigerator. A series of eight dilutions were made from the standard dust extract No. 1, as shown in Table I. Of these 0.5 ml was poured over the serum-agar in each of two tubes.

Tests were read after forty-three and ninety-six hours, and the distances of penetration of two precipitation bands measured. The averages of these are recorded as D in the table. From these the penetration rates were calculated by dividing the distance of penetration by the square root of the time. These are recorded in the table as P.

Three precipitation bands were seen (Fig. 22), one fast moving, extremely faint and without a clearly defined leading edge, the second moving at not much more than half the rate of the first but heavy and with a sharply defined leading edge. The third was largely obscured by the dense trailing zone of the second and could not be measured. Bands 1 and 2 are believed to correspond to *a* and *c* of the plate patterns in spite of their different relative positions.

The values of the penetration rates (P) when plotted against the logarithm of the concentration tend to form a straight line (Fig. 23), which may be taken as a standard graph for extract No. 1 with its standard antiserum P 30. The extract itself, though actually the standard, may be discarded because it can always be reproduced by assaying a new extract against the standard serum. Or it may be used as a working standard for standardizing new extracts and testing new antisera as they are prepared. It can, of course, be used with any antiserum that is shown to produce the same precipitation pattern with it as did the standard serum.

SUMMARY AND CONCLUSIONS

The antigenic analysis of a number of dust extracts chosen for their similarities and diversities of origin shows that all have at least three

antigens which give precipitation bands with antibodies of their homologous antisera or of some other dust extract. One of these bands is nearly always much more prominent than the others. It can, therefore, be concluded that these dust preparations all have one major antigen and two or more minor antigens.

A comparison of the precipitation patterns of these dust preparations

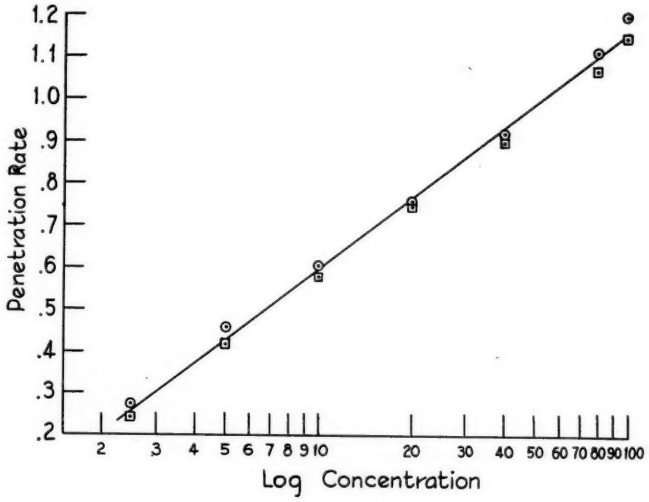


Fig. 23. Graph of the penetration rates for band 1 of house dust No. 1, plotted against log concentration (in M u/ml), readings at forty-three hours and at ninety-six hours.

showed that the major antigen is common to them all, but the minors are not always, though they frequently are.

Dust of diverse origins often may be shown to have the same antigens, but these occur in very different proportions. On the other hand, dust preparations made from material from the same or similar sources have been found to have the same antigens in very nearly the same proportions. On the whole this is in harmony with Maunsell's hypothesis quoted above.

Antiserum developed against upholstery dust, No. 1 was shown to give weak precipitation bands with the extraneous allergens, danders of horse, cat, cattle, dog, rabbit, and human serum. Of these, only the reaction to human serum is certainly biologically specific, and indicates material of human origin in dust No. 1. The reaction to rabbit dander could scarcely be specific because that would require a rabbit to develop antibody to its own dander. The reactions to the other danders may or may not be specific. However, they are not due to a common contaminating substance because they give precipitation patterns of non-identity.

Three human sera from highly dust-sensitive patients with transferable dust reagins failed to precipitate with the standard dust extract. Instead, two of them precipitated with the rabbit antidust serum that was included in the plates for comparison with the human antisera.

Standardization of dust extracts may be accomplished by setting aside in lyophilized state, pooled antidust rabbit serum made with a selected dust extract. Its precipitation pattern and graph of its penetration rate in relation to concentration will then serve to identify and assay any unknown dust extract in terms of the designated standard.

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Patients who are being treated for hay fever and other allergies frequently complain of frequent urination.

According to an article in the *Diuretic Review* for June, 1954, recent studies indicate that certain commonly used antihistaminic drugs may be responsible, as they have a diuretic effect.

The *Diuretic Review*, a new publication by Lakeside Laboratories, Milwaukee, distributed to physicians and educators, devotes its first issue to research and current trends in cardiorenal and electrolyte therapy.

FUTURE RESEARCH IN ALLERGY

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IN 1925, when I began my first experiments in the field of allergy, there were only a small number of doctors specializing in the treatment of allergic diseases. Very few investigators were interested in problems of hypersensitivity to chemical substances and most of them confined their work to the relationship of immunity and allergy to infectious agents. At that time, barely thirty years ago, when investigators interested in the broad field of allergy came together to discuss their problems and results, the meeting place was virtually a House of Babel. Each investigator had his own definition of the technical terms then currently in use. There was no agreement about the meaning of such words as idiosyncrasy, sensitivity, hypersensitivity, hypersensitiveness, incubation period versus sensitization period, acquired immunity, desensitization, and many others. Consequently, every speaker started in with an *exposé* of his own concepts of terminology.

Today many allergists are engaged in active research in allergy in all parts of the world, but the confusion over terminology has by no means diminished. In fact, today's best informed allergists have not reached unanimity as to whether allergy and acquired resistance are inter-related. The most diversified meanings are attached to the terms anaphylaxis and, especially, idiosyncrasy, and there is, to cite still another example, very little agreement in the literature as to the definitions or, in fact, the usefulness of the terms atopic and non-atopic allergy. Even the most ardent defenders of the concept of atopy disagree as to what it entails or excludes. Another moot point is the difference between the contact type of sensitization and the tuberculin or delayed type; the latter form is ill-defined and quite unclear to many allergists.

In his latest edition of the "Pathogenesis of Tuberculosis," Rich complains vigorously about this state of affairs. "There is perhaps no clearer example of the confusion in thought and concept than that afforded by the literature dealing with hypersensitivity and of allergy," he exclaims, "As for the term 'allergy' that word has become so debauched by indiscriminate usage, that it would be fortunate, indeed, if it could be dropped completely from the vocabulary of science." More than ten years before Rich's indictment, in his excellent book on "Dermatologic Allergy" which is unfortunately out of print, Sulzberger wrote "The word 'allergy' may perhaps not be here to stay; and the specialty now known as 'allergy'

From the Research Department, Ciba Pharmaceutical Products Inc.
Dr. Mayer is an Associate Fellow of The American College of Allergists.
Presented at the Graduate Instructional Course, American College of Allergists, Miami, Florida, April 7, 1954.

may not be a permanent institution among the branches of practical medicine. But, by whatever name one may come to call certain phenomena, by whatever boundaries and nomenclatures one may choose to delimit fields of medical practice, the majority of the phenomena of allergy will inevitably continue to be of both theoretical and practical interest—for they are based upon intrinsic attributes of living tissues." Allergists would be very greatly disturbed were they forced to seek new terms for their specialty and for themselves as specialists. But, they themselves could contribute much to restoring faith in the scientific precision of their terminology and for the justification of their specialty.

It is not possible to discuss in one brief paper future research in the whole wide field of allergy. In his opening remarks to the Second European Allergy Congress in Copenhagen, our past president, Fred W. Wittich, discussed the impact of allergy on general medicine and comforted his listeners with the remark that allergy is not so much a subspecialty of internal medicine, but that internal medicine is rather a part of allergy. Indeed, allergy covers an enormous field of medicine and includes a considerable proportion of internal medicine—pediatrics, dermatology, otorhinology, cardiology and even psychiatry.

The allergist, as a medical specialist, has taken for himself only a small slice of the large field of allergy when he specializes in the treatment of the so-called allergic diseases. He considers as his main interests those allergies elicited by non-living material and only takes a secondary interest in allergic reactions produced by living organisms, as is the case in immune reactions associated with bacterial, mycotic, protozoal, helminthic and epizoic diseases. The allergist, furthermore, is only partly interested in the study and treatment of allergic reactions brought about by chemical substances contained in living organisms. We shall not consider all allergic reactions that occur during an infection or are produced as the result of diagnostic procedures, such as skin tests and tests made with bacterial proteins to determine the presence or absence of a bacterial, mycotic or protozoal infection. Such reactions may also occur during the treatment of such diseases with bacterial proteins. In other words, we shall confine our attention to the field centered around the so-called "allergic diseases."

Any research on the subject of allergic diseases and all problems connected with it logically deal with two aspects: first, the clinical aspect involving diagnosis, development of the disease and treatment; secondly the theoretical side concerning etiology, physiology and pathology. There is little doubt that with respect to the clinical aspects of allergy, especially the diagnosis and treatment of allergic and allied diseases, there are many unsolved problems. It is in most cases not too difficult to recognize the allergic nature of pathological processes. The case history is often revealing and the presence of definite sensitization periods, absence of primary irritating properties in the causative agent, positive skin reactions and

typical clinical manifestations point to the correct diagnosis of an allergic state. Most, although not all, cases of contact dermatitis, urticaria, bronchial asthma or hay fever are allergenic in nature. But there exist, besides these classical diseases, certain pathological processes which are not classified as allergic diseases although they present many symptoms or aspects suggestive of allergic origin, and the question arises whether such diseases may not belong to the hitherto unrecognized group of allergic diseases.

There is, for instance, lupus erythematosus, the butterfly or bat's wing lupus. This serious disease has long been attributed to a number of causes, as for example, to an infection with tubercle bacilli, streptococcal toxemia or other specific organisms, with a virus, to an intolerance to light, or to an allergy. Indeed, acute eruptions of this disease have been observed after serotherapy and sulfonamides. Lately, it has been observed that prolonged administration of unusually large amounts of certain remedies, such as penicillin or Apresoline,® are capable at times of producing a symptom complex closely resembling lupus erythematosus. Certain investigators feel that all these drugs do not produce the real disease, but a lupus erythematosus-like reaction to Apresoline. They may act like quinine which sometimes produces a scarlatina-like dermatitis medicamentosa or scarlatina-like eruption. Lupus erythematosus as a side reaction has become very rare since it has been possible to lower considerably the therapeutic doses of Apresoline, especially when used in combination with Serpasil. However, the conditions under which the lupus erythematosus-like side reaction did appear as a result of the administration of various drugs, pointed to the possibility that it was of allergic origin. Indeed, it appeared only after a long interval during which time the drug was well tolerated and then only in a relatively small percentage of many patients treated in the same manner.

These facts also suggest that the idiopathic lupus erythematosus may be an allergic disease. The cases of lupus erythematosus associated with drug therapy have been connected with various related disease entities such as the exanthematic lupus of Kaposi, the disease of Libman-Sacks, periarteritis nodosa and others.

In a number of cases, the lupus erythematosus, or if you prefer, the lupus erythematosus-like side reactions were accompanied by symptoms of rheumatoid arthritis. The evidence that this latter "disease" is the consequence of an allergic sensitization is even more substantial. Rheumatoid arthritis has long been attributed to an allergy to toxins of streptococci. But, Rich has shown in a series of brilliant pathological analyses and experimental studies, that all lesions pathognomonic for rheumatoid arthritis are present in patients who have died from a sulfonamide allergy. Rich was able to reproduce similar pathological reactions in rabbits after sensitization to horse serum. It has been proven that symptoms of collagen

disease, degeneration of the media of the capillaries, Aschoff's bodies and other characteristic signs of rheumatoid arthritis are observed in a number of typical allergic insults. Nevertheless, all this does not justify the conclusion that the idiopathic lupus erythematosus or the idiopathic rheumatoid arthritis, when they occur without any detectable cause, are allergies. There is, indeed, an important difference between the idiopathic lupus and the idiopathic rheumatoid arthritis, and the side reactions of identical clinical aspect. All cases of rheumatoid arthritis and lupus erythematosus which occurred as side effects of certain drugs have regressed completely as soon as the drug was omitted—only a few cases of extreme allergy to sulfonamide have caused rapid death. Idiopathic lupus erythematosus, on the contrary, is in almost every instance a chronic and fatal disease, and idiopathic rheumatoid arthritis is a constantly progressing process in spite of long remissions. This is perhaps only a quantitative difference; the idiopathic diseases may be progressing and fatal only because the allergen, unknown and therefore ignored, continues to be present and to act.

Lupus erythematosus or rheumatoid arthritis call to mind a fact discovered a few years ago with respect to agranulocytosis. This disease was considered for a long time as an idiopathic disease. Because of the ever-present ulcerative tonsillitis, at least in the terminal stages, agranulocytosis was considered by many clinicians to be of infectious origin. It remained for Kracke to demonstraate that the infection was only a secondary terminal process and that the actual cause of the disease was an intolerance toward certain chemicals used as remedies, especially Pyramidon and other aromatic substances capable of being transformed into quinones. Agranulocytosis is a hypersensitivity disease; whether it is based upon a truly allergic, specific hypersensitivity constitutes a problem for future research in allergy.

There are a number of other diseases which, like agranulocytosis, may in the future be admitted to the family circle of allergic diseases. Multiple sclerosis has been successively attributed to a virus infection, to spirochetes, to bacterial infections, endocrine disturbances and allergy. Experimental data assembled in recent years point to the possibility that an allergic factor is involved in the origin of multiple sclerosis. Similar discrepancies still exist as to the pathogenesis of sarcoidosis. This disease, long associated with tuberculosis, is now being considered by many authors as another allergic disease of unknown origin.

The elucidation of the possible allergic nature of these different diseases is an experimentally tempting problem. This question is important also from a more general point of view and may, whether we like it or not, further complicate the concept of allergy. It may, indeed, lead to an extension of the present limits—already quite large—of the field of specific hypersensitivity.

In order to recognize the allergic nature of a pathological process, Doerr, years ago, established four criteria which in spite of many recent

contributions to our knowledge of allergy, are still pertinent and valid. These criteria, as you certainly recall, are:

1. Deviation from the norm as compared to the previous behavior of the individual or, in the case of innate allergy, to the behavior of other individuals of the same species.
2. Specificity of the hypersensitivity, that is, mono-specificity or poly-specificity.
3. Independence of the clinical reactions from the chemical and pharmacological properties of the causative agent. The clinical symptoms must be reproducible in a typical anaphylactic experiment on animals or man. This third criterion includes today, the experimental reproduction of other allergies such as contact dermatitis, etc.
4. It is necessary to establish the presence of "reagins" in the reactive cells which can be defined chemically. The proof is considered as established if the passive transfer of the reactivity upon normal individuals has been successful.

No doubt, in all these diseases discussed above, such as lupus erythematosus, sarcoidosis, et cetera, the first criterion is always fulfilled: The disease develops only after a prolonged incubation period which may last many months and then only in a small proportion of the total number of individuals so treated. The same holds true for the second criterion. The reactivity is specifically directed against the causative agent and there is a specific cross-reactivity. The symptoms disappear after withdrawal of the drug but in many cases promptly reappear when the drug or chemically related substances are administered.

The independence of the symptoms from the chemical and pharmacological properties is also obvious to each of the cases under discussion. Lupus erythematosus and the other diseases have not yet been reproduced in animals except for the above-mentioned experiments reported by Rich, and antibodies have not been detected. This is an important task for the future. But does the failure to detect antibodies exclude the possibility that lupus erythematosus, agranulocytosis, sarcoidosis, et cetera, are allergic diseases? We had to wait almost twenty years before Landsteiner and Chase demonstrated that the postulated sessile antibodies of contact dermatitis or of the delayed reaction actually existed. But during these twenty years and longer, no one ever questioned the true allergic nature of contact dermatitis or the tuberculin reaction even before the existence of sessile antibodies was established by the passive transfer of white blood cells from a sensitized individual.

However, as long as the evidence has not been established beyond doubt, we must accept the equally good evidence that lupus erythematosus, agranulocytosis and sarcoidosis are not allergic diseases, but are only the result of primary toxic reactions which mimic, in their occurrence, an allergy. Such reactions exist indeed. We know of primarily toxic, non-

allergic processes which suddenly occur, after a so-called incubation period, only in a few of many equally exposed persons. An example is the sometimes fatal intoxication with potassium chlorate, a now obsolete medicament, which has been used over and over again and in substantial doses without producing ill effects. A number of sudden fatal intoxications have occurred after otherwise nontoxic doses, which closely resemble allergic processes but are definitely non-allergic. It was indeed found that the patients who experienced these toxic effects metabolized the potassium chlorate much more rapidly than did normal individuals. The result was a rapid and considerable formation of methemoglobin and consequent anoxemia, a process which has nothing in common with allergy.

It is not necessary to look for problems exclusively among the more uncommon diseases; even in the field of the well-established, usual allergic diseases, there are numerous unexplored and important problems. I shall mention only a few which seem to me to be particularly interesting. A number of years ago, I had an opportunity to investigate the alternation, in the same patient, of allergic skin reactions, especially neurodermatitis and bronchial asthma. Such a double allergic manifestation may occur when the patient becomes simultaneously or successively sensitized to two or more different compounds which have affinities to different receptive cell systems or, in another instance, when his different receptive cell systems become sensitized to the same allergen. Most outstanding in producing such a multiple allergy is the hair and fur dye, para-phenylenediamine. Indeed, I observed and examined many fur dyers who first reacted, upon impact of the dye, with a contact dermatitis, which then changed into a neurodermatitis. When these patients later acquired a superimposed p-phenylenediamine asthma, their atopic eczema and asthma alternated. Many even maintained their dermatitis in order to remain free from asthma. Such cases occur also with other allergens. A study of the transformation of contact dermatitis into atopic dermatitis and the successive or concomitant sensitization of the epidermal and vascular apparatus may shed new light on the relationship between atopic and nonatopic allergies. It is not known whether the humoral and sessile antibodies involved in these various manifestations are chemically different, why they are formed or released at different intervals, perhaps one at the expense of the other, or whether the factors responsible for the alternation are secondary to the allergic process proper. Closely related to this question is the problem of why certain chemically well-defined substances preferentially elicit different forms of allergies. Azodyes, many allergenic plant constituents, metal salts, among others, produce almost exclusively, the contact type of allergy, even when they reach the epidermis from within the body. They practically never cause asthma. Other substances, such as ipecacuanha, or foreign proteins generally produce atopic dermatitis or asthma, but practically never contact dermatitis. A few compounds, among them the notorious p-phenylenedia-

mine, are capable of producing all forms of allergic sensitizations and manifestations.

Epstein has formulated an interesting theory to explain the different activities and the production of different antibodies by various chemicals. Since it seems established that a substance may sensitize only after combination with a carrier, which in most instances is a protein, Epstein suggests that the prominence and chemical nature of the proteinic carrier may play an important role in the localization of the ensuing allergy. Contact allergens most likely combine with proteins of the epidermis and thus elicit particular antibodies which direct or restrict the allergic process to the epidermis as contact allergy.

Another important, still unexplored, point is the following: Most allergenic substances elicit the common variety of allergic reactions, such as dermatitis, urticaria and asthma; and the lack of correlation between the chemical nature of most allergens and the allergic disease they elicit is one of the basic credos of allergy but is also our cross in diagnosis. But there are a few substances that produce allergies of a most characteristic aspect, namely, the so-called fixed drug eruptions (Brocq). These are allergic reactions which again and again recur on the same circumscribed parts of the skin and are quite distinct from other forms of allergic manifestations. Many substances are capable of producing such fixed reactions, but the best known are phenolphthalein, antipyrine and phenacetin. A great number of basic studies have been made on these fixed eruptions which may have importance in the study of the above-mentioned diseases of doubtful allergic nature.

A few other allergic skin eruptions, besides the phenolphthaline exanthema, readily reveal or at least point to the causative agent, as for instance the bullous eruptions after iodides or the extended scarlatiniform dermatitis medicamentosa after quinine. The study of these reactions is quite important for the better understanding of the role of the antigen in the site, the form and the course of an allergic side effect.

Research, in the relationship between chemical constitution and allergenic properties belongs in the same domain. I mention this problem particularly because it represents a very promising, interesting and important type of research and one that can be performed with the simplest of allergic methods, namely, the various skin testing methods. As just mentioned, the sensitizing properties of a chemical substance are generally explained by the theory that they must combine with a carrier-substance of high molecular weight, generally a protein. There are, however, many simple chemicals which are known as potent allergens but which are, as such, unable to combine with a carrier. These substances are, it seems, not the direct allergens, but only the parent substances from which the direct allergen is formed during the metabolic attacks within the organism. The metabolic oxidations and reductions lead to intermediates which are then able to combine with a carrier and thus serve as the actual allergen. It

frequently occurs that a substance which is known to be highly allergenic for a patient does not elicit any positive skin reaction by any of the usual test methods. This may well be due to the fact that this substance is only the inactive precursor of the true allergen which may be formed in the liver or elsewhere during its metabolic changes.

We need continued research on cross sensitization, particularly to substances which are known to be powerful contactants. The introduction in our daily lives of new dyes, plastics, insecticides and drugs all of which have many chemical groupings in common, constantly create new sources of allergies and, by cross reactions, tend to perpetuate old and long established allergies. It is therefore necessary to recognize the chemical relationship of all these new compounds with older, known allergens and to replace strong sensitizers by other substances which are as useful but less allergenic. Prophylaxis of allergic diseases is identical with the recognition of the allergen.

During the preceding discussions, we have dealt almost exclusively with allergic reactions which take place on or in the skin and the diagnosis of most of these diseases which is more a dermatological problem than one which concerns the allergist. Indeed, allergy and dermatology are two specialties which overlap considerably and many allergic patients have considerable difficulty in deciding whether they should consult the allergist or the dermatologist. At this point, I want to make a few remarks on this relationship, which is not always simple, between allergists and dermatologists. The allergist must bear in mind that dermatologists have contributed enormously to our knowledge of allergy. Dermatologists such as J. Jadassohn and Bruno Bloch have established the scientific bases of many important allergic reactions of microbial allergies as well as chemical allergies. As a matter of fact, most of the ground work in allergy was performed in dermatologic clinics.

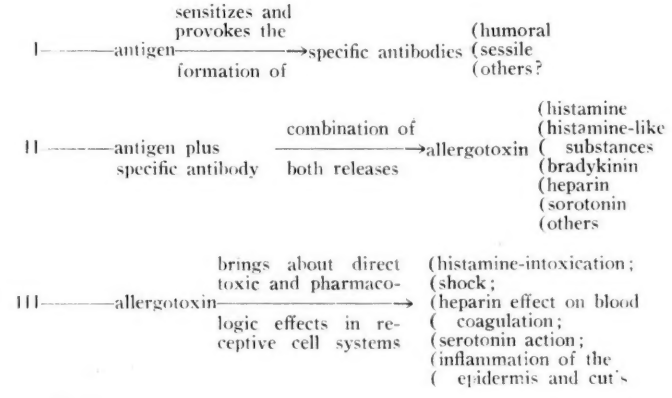
The scope of dermatologic allergy is much broader than that which the allergist usually attributes to his own field. Dermatologic allergy is concerned not only with the skin allergies to non-living material but also to the enormous field of allergy to infection. Indeed, the skin is the mirror of practically all infectious allergies: of the acute infections such as measles, scarlatina, small pox, etc., and of all the chronic infections such as tuberculosis, leprosy, syphilis, blastomycosis, etc. The dermatologist's more exclusive domain extends to allergies to infections which accompany infections of the skin proper, with fungi, yeasts, bacteria and epizoas and the very interesting and important field of the so-called ids.

It is not possible to separate the study of the allergy to infection from the allergy to non-infectious, non-living agents, at least in its theoretical implications. The allergist today unduly neglects this field. This is at least partially explained by the fact that he has little access to this group of diseases. I have always deplored the lack of collaboration between allergists and dermatologists. There is no doubt that the allergist can

greatly profit from a better understanding of the many problems of dermatology. The reverse is also definitely true.

If we now consider the second aspect of future allergic research, namely that which is concerned with theoretical questions, we soon realize that we are entering a virgin forest in which we can barely see the woods for the trees. Here, the allergist should not confine his interest to theoretical questions related to the restricted field of allergic diseases but rather, he should investigate the whole field of immunology. Indeed, most of the basic phenomena associated with bacterial allergy are identical with those observed in allergies to pure chemicals and their study can show the way to the solution of many of the allergist's practical problems and vice versa. Many procedures which have been successfully applied in the study and treatment of bacterial allergies were unsuccessful when applied to allergies to non-living material. So far, we have not done too well in desensitization in allergic diseases, particularly in contact dermatitis. We have been highly successful in passively transferring the acquired immunity to bacterial infections, but we have failed in similar attempts in the field of allergic diseases. Did we fail because our reasoning was faulty and because the followers of the dualistic school of thought are correct in believing that acquired immunity to infection and hypersensitiveness are two entirely different processes? Or, did we fail only because our approach was inadequate but our reasoning, based upon the unitarian belief, was correct that hypersensitivity and acquired immunity are parts of the same process?

Let us frankly admit how little we know of the allergic process. We recognize this if we express the allergic reaction by the three short formulas, I, II and III, well-known to all of us:



In these three formulas, our allergic credo is contained. It is known by heart by every allergist as well as he knows the alphabet or multiplication table. But, if we were to apply the Cartesian method of questioning the

evidence of each of the many steps involved, then we must soon confess that no more than a few have been established. All we know for certain is that (1) certain allergens bring about the formation of antibodies, (2) it is possible to determine the presence of humoral and sessile antibodies, and (3) in certain allergies, and in only a few, histamine is the active allergotoxin. All the rest are deductions, analogies, theories and subject to future verification or rejection. It is not the purpose here to enumerate the important theoretical problems that still await a solution, and I do not want to deal with the role allergy may play in normal physiology and the maintenance of life. I only would like to single out a few of the questions that have become more acute in the light of recent developments.

Histamine, released in excessive amounts, is the cause of anaphylaxis and related atopic allergic manifestations. It is important to know how histamine is released from histidine and other bonds; whether histamine has any physiologic role in metabolism, or serves only as a protective agent to be released or used in the event of certain emergencies or whether, as is currently believed, its release during the antigen-antibody reaction represents an unfortunate autotoxic process.

Recent research initiated in England seems to throw some light on this problem. It has been known for a long time that a single injection of certain substances produces reactions identical with anaphylactic manifestations. But they occur without previous sensitization. In certain animals, a single intravenous injection of egg white or blood extenders such as PVP or dextran, or high molecular polymers such as Tween 80, will produce urticaria and shock. Peptone shock and the action of certain snake venoms belong to this group. On the other hand, the intradermal injection of certain simple chemical substances, such as atropine or morphine, produce urticarial reactions that are identical with the triple reaction of Lewis produced by histamine. Lately, McIntosh and Patton have demonstrated that all these various chemicals release histamine from certain organs in large amounts which result in histamine intoxication, urticaria and shock. During this reaction, certain organs may become depleted of histamine for several days or even weeks and if the depletion takes place in the shock organs of previously sensitized animals, then a challenge injection of the specific allergen fails to produce allergic manifestations. These recent studies constitute not only important steps toward a better understanding of the mechanism of certain allergic reactions, but may indeed pave the way to a new and important therapeutic approach to allergy.

Histamine, as we have learned, is not, however, the only allergotoxin released when "antigen meets antibody." Other substances released during the allergic process must be responsible for most cases of bronchial asthma, dermatitis and migraine. It is urgent to explore the nature of these substances if we want to find specific antidotes. One way to accomplish this is to study the enzymatic processes involved in the liberation of allergotoxin

which is still in its initial stages. So far, we only have dealt with the allergic chain reaction at the first and the last link, namely, the antibody and the allergotoxin. Studies of the enzymatic process, initiated by Rocha e Silva, Zeller, and others are concerned with intermediate links between these two ends.

There are other theoretical problems too numerous to mention. However, I want to draw your attention to a point which is considered by many investigators as of secondary importance only, the question of the scientific tools with which to tackle our allergic problems. Tools are the fuel of scientific research. Allergy research received its greatest impetus when Jadassohn, almost sixty years ago, introduced the patch-test, von Pirquet the intradermal and scratch test, Prausnitz and Kustner the methods of passive transfer, Schulz-Dale the method of *in vitro* testing on sensitized smooth muscles, and B. Bloch the experimental sensitizations of guinea pigs' skin. New tools are now being introduced which may be instrumental in solving many of the urgent problems. I only mention paper chromatography which may help in detecting antibodies and the allergotoxin, tracer elements, which may localize antigens and antibodies in the organs. An interesting new tool has been lately introduced by Selye, namely, the air pouch in experimental animals. He insufflates a certain amount of air into the subcutis of a rat and injects into this air bubble, an inflammation-producing substance such as croton oil. The pouch becomes fixed and subsequently fills with a serous cell-containing exudate. This simple technique has already, in Selye's laboratory, furnished important results on the role of the reticulo cells in inflammation. The application of this simple technique to the study of antigen-antibody reactions may provide answers to many of our unsolved questions.

Why do we insist so much upon the importance of theoretical research? It is true that many of us indulge in theoretical research in order to satisfy our scientific curiosity and this is certainly an important incentive to happiness. But, this is only a minor reason. We know from experience gained from all other disciplines of medicine that it is not possible to devise a logical therapy of any disease unless the basic causes and mechanisms of the pathologic process of this disease are recognized Unless we have found the microorganism which causes a certain infectious disease, unless we know the conditions under which the organism multiplies and under which the host responds, we cannot cure the disease. To this end we must find ways to reproduce this disease in laboratory animals so that we can study the development of the disease and screen substances for their ability to cure it. If we want to cure allergy, we must be able to produce it in animals and recognize all the pathological pathways which lead to the allergic manifestation. Unless we have recognized the chemical nature of the various allergotoxins released in the antigen-antibody reaction which precedes asthma, migraine and contact dermatitis, all our therapeutic attempts remain symptomatic and empirical.

The only known anti-allergic agents which act on the very source are the antihistaminics. The discovery of this group of therapeutic agents is the best justification for extensive theoretical research. Only after Dale had shown that histamine is the principal offender in anaphylaxis, and it became apparent that histamine is released in large amounts during allergic manifestations, did Bovet conceive of the idea of searching systematically for substances that would counteract histamine and thus nullify its deleterious effects in the allergic reaction.

There is a very important scientific problem connected with any theoretical research and which we may touch briefly, since it concerns most vitally allergy research—the problem of research laboratories. Contrary to clinical research, basic research on any problem including those of allergy, needs suitable laboratories, equipped with modern apparatus, and staffed with well-trained specialists. The time has passed when a few test tubes, pipettes, a centrifuge and a water bath are sufficient for the investigation of basic problems of immunology and allergy. Today's research in allergy has shifted largely to pharmacology, enzymology and biochemistry. Unfortunately, the problem of suitable laboratories for allergy research and of allergists skilled in modern techniques, is a very difficult one. Of all branches of internal medicine, allergy units possess the least adequate research facilities. Any internal, pediatric, endocrine, and many dermatologic, clinics have modern research facilities. But, I know of only a very few modern allergy laboratories, at least in this country, and even these are quite modest. It is, therefore, unfortunate, though understandable, that at present little theoretical work in allergy does not emanate from allergists themselves and from allergy units, but rather from physiologists, pharmacologists and biochemists who have developed an interest in this field. Furthermore, many allergists are only beginning to realize that the theoretical bases of his field have shifted and that he must acquire a wider background. Too many allergists are still entangled in the field of immuno-serology and find their way only with difficulty in the expanding field of immunochemistry.

No doubt much has been done in allergy research within the past fifty years, but only a very small distance of the way to the better understanding of allergic reactions and to the rational therapy of allergic diseases has been covered. Truly, there is no scarcity of problems for future research in allergy.

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CHRONIC ULCERATIVE COLITIS AND REGIONAL ENTERITIS—THEIR ALLERGIC ASPECTS

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SINCE 1938 our studies[9] increasingly have indicated that atopic allergy is the probable primary cause of chronic ulcerative colitis and regional enteritis. An eczematous-like reaction involving all layers of the bowel seems responsible. As in eczema and other clinical allergies, foods and inhalants, especially pollens, have been incriminated. Drug allergy has been recognized. Bacterial allergy has not been evident. When allergy is the sole cause, anti-allergic therapy alone controls the symptoms. When infection, anemia, or complications are present, their control also is required. Our experience supports food allergy as the major cause, as first reported by Andresen[1] and later by Mackie.[6] During the last thirteen years we have obtained increasing evidence that pollen allergy,[9] alone or in association with food allergy, also is causative.

Favoring allergy are the following observations:

1. Gastrointestinal allergy[2,14,16] is common, as has been revealed especially with the adequate use of our elimination diets. The colon and the small bowel may be the only shock organs of allergy.

2. Localization in the colon and small bowel, especially in the distal portions, occurs in other tissues in other manifestations of clinical allergy, as in atopic dermatitis.

3. The spreading tendency in chronic ulcerative colitis and regional enteritis also occurs in allergic dermatitis.

4. Remissions and exacerbations occur in other clinical allergies, such as allergic eczema and bronchial asthma. Increase in the pollen seasons, with absence or decrease in the winters, suggests pollen allergy. Increase in the late fall to early spring, with decrease or relief in the summers, suggests food allergy[10] or at times indoor inhalant allergy, to which there is increased exposure in the winter half of the year. Decrease or absence of symptoms in some pregnancies is explained by resultant refractoriness to causative allergens, especially foods.

5. Fever at times is due to food[11] and drug allergy, although secondary infection is the usual cause.

6. The erythema, granulation due to multitudinous minute papulovesicular lesions arising from the involved capillaries, and the serous discharge and friability of the mucosa in chronic ulcerative colitis also occur in atopic dermatitis. The microscopic edema, round cell, and in

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TABLE I. CHRONIC ULCERATIVE COLITIS

Statistics on 138 Patients

Hospital Cases: 88		Office Cases: 50
Females: 96		Males: 42
Age of Onset	27.4 years (8 to 71 years)	
Age at First Visit	31.9 years (10 to 78 years)	
Previous Duration	Average: 4 years (½ to 40 years)	
Degree of C.U.C.:	Grade 4: most severe	23.9%
	Grade 3:	39.0%
	Grade 2:	30.4%
	Grade 1:	2.8%
History of Probable Food Allergy		50.0%
History of Probable Milk Allergy		30.4%

TABLE II. CAUSES OF C.U.C. AS INDICATED BY RESULTS OF ANTI-ALLERGIC STUDY AND THERAPY

Food allergy alone	45%
Food allergy alone (questionable)	3%
Pollen allergy alone	3%
Pollen allergy and food allergy	10%
Pollen allergy and questionable food allergy	9%
Food allergy and questionable pollen allergy	15%
Questionable pollen allergy and questionable food allergy	7%
Undetermined probable causes	8%

regional enteritis the eosinophilic infiltration, the vascular thromboses, necroses, and later perforations, and changes in the ground substance can best be explained by allergy.

CHRONIC ULCERATIVE COLITIS

Analysis of 138 cases, whose histories were taken and studies and treatment were conducted by the writers in the last sixteen years, is summarized in the charts. The predominance of females, the average onset in the twenties although no age is exempt including infancy, the predominant severity of grades 4 and 3, the usual x-ray evidence in the distal colon, the not infrequent terminal ileitis and pseudopolyposis, and the family and personal histories of allergy in only approximately 25 per cent of the patients showing that the colon often is the only shock organ of clinical allergy are shown in these statistics. Other than fever, various recognized complications occurred in thirty-seven patients. Of eighty-three patients with fever,[11] 43 per cent were controlled without sulfonamides and antibiotics. This favored atopic allergy alone as the cause. Normal pregnancies in fourteen patients, with two in three patients, occurred. Caesareans were done in five patients. There was one miscarriage and one baby was dead of erythroblastosis at term. Cancer of the colon occurred in only one patient. This infrequency may have been due to the reduction or absence of the constant irritation of chronic continuing allergy by the anti-allergic control of the colitis in most of these patients.

TABLE. III. FAMILY AND PERSONAL HISTORIES

In 138 Cases of C.U.C.

1. Family History (one or more manifestations in only forty-eight patients)
   - Gastrointestinal symptoms 17%
   - Bronchial asthma 17%
   - Perennial nasal symptoms 12%
   - Headaches 8%
   - Eczema 9%

2. Personal History of Possible Allergy (one or more manifestations in only forty-seven patients)
   - Bronchial asthma 5%
   - Hay fever 9%
   - Perennial nasal symptoms 7%
   - Eczema 8%
   - Hives 4%
   - Gastrointestinal symptoms 12%
   - Headaches 9%
   - Constipation 11%
   - Pruritus ani 2%
   - Canker sores 5%

TABLE IV. COMPLICATIONS

(Other Than Fever in Thirty-seven Patients)

Arthritis	3.0%
Cancer of colon	.7%
Erythema nodosum	3.0%
Fever (no antibiotics or sulfonamides given in 32 patients)	60.0%
Fistula, rectal	6.0%
Hemorrhage	3.0%
Necrotic reaction to vaccine	3.0%
Parotitis	.7%
Perforation	4.0%
Pyoderma gangrenosum	1.5%
Recto-vaginal fistula	8.0%
Thrombophlebitis	4.0%
Pregnancy (2 in each of 3 patients)	17
Miscarriage	1

TREATMENT

As in all atopic allergy, food and inhalant allergies have been persistently studied.

FOOD ALLERGY

Food allergy was suggested by perennial symptoms, its tendency to be regularly recurrent, its activation at times by menstruation and during the fall, winter, and early spring months.[10] The latter was evidenced in one case of twenty-five years' duration whose symptoms only occurred from late fall to early spring and were well controlled by the elimination of allergenic foods. The family and personal histories usually are negative for allergy, and skin tests by the scratch method rarely are positive in these patients. The diet history often reveals a definite or even a lifelong dislike or idiosyncrasy for foods, as in 50 per cent of our patients. Such a history is probably significant in 30 to 50 per cent, especially in regard to milk, to which there was a positive history in 30 per cent of our series. A positive diet history,[12] however, infrequently

TABLE V. SKIN REACTIONS, X-RAY, AND OTHER FINDINGS

Skin Reactions by the Scratch Method

Foods	Positive in 15 patients (1 to 5 +)
Pollens	Positive in 23 patients (2 to 8 in 8 patients)
Dust	Positive in 6 patients (1)
Animal emanations and miscellaneous inhalants	Positive in 8 patients (1 and 2 +)

C.U.C. Revealed by X-Ray of Colon

Descending colon and sigmoid	46.0%
Transverse and distal colon	25.0%
Entire colon	26.0%
Ascending and transverse	1.5%
Pseudopolyposis	9.0%
Ileitis	11.0%
Proctoscopic evidence of C.U.C. with negative x-ray findings in	7.5%

reveals all allergenic foods and often is negative when food allergy is responsible.

Thus diet trial is required for the study of food allergy, for which our fruit- and cereal-free elimination diet plus rice[12] may be used in mild or moderate cases. Until relief occurs, pureed vegetables are advisable. If diet history or use of the diet indicates possible allergy or indigestion to any foods in the diet, they are eliminated. Thus soy and other legumes often have to be deleted. When milk allergy is definitely suspected or present, beef should be excluded. In severe and especially fulminating cases, a minimal fruit-free elimination diet is desirable, containing lamb, white potato, tapioca, salt, sugar, water, synthetic vitamins, and calcium.[13] Rice also may be added, with or without potato. Nutrition and weight must be protected. At times the writers' meat formula[9,12] containing extra strained meat and extra cane sugar to furnish up to 2,500 calories and up to 100 or 120 grams of protein, can be drunk or, if indicated, intubated, alone. It may be given in moderate amounts every two to four hours for several days, with the later addition of other foods in the above diet. As stressed in previous publications,[12,14,15] traces of eliminated foods must not be taken, and maintenance of weight is most important. Since food allergens enter the body through the lungs, the inhalation of foods eliminated from the diet must be minimized or prevented. Thus severe chronic ulcerative colitis had been absent in a woman for four years with a fruit-free elimination diet plus rice and egg. Then against orders she canned a box of tomatoes, inhaling but not ingesting them. Bleeding and diarrhea started that night, increasing along with fever in the next three days. With nine transfusions and the minimal fruit-free elimination diet, recovery gradually occurred in three weeks. Then, with perfect control of her colitis, two years later she camped with her family in a ripe apple orchard. Bleeding again developed in a few hours. She left soon afterwards, and bleeding and moderate diarrhea disappeared in five days. Another patient's severe colitis was well controlled by her elimination diet and pollen therapy except for three to five loose daily stools. Formed stools developed finally when she avoided the smell of

TABLE VI-A. CO-OPERATION AND RESULTS

Time of Co-operation in 138 Patients

Average: 3.7 years (Total: 488 years)	
From 10 to 15 years	13 patients
From 5 to 10 years	22 patients
From 1 to 5 years	50 patients
From ½ to 1 year	18 patients
From ¼ to ½ year	15 patients
From 1/25 to ¼ year	14 patients
Death in first 2 weeks (before 1946)	6 patients

Even though time of co-operation was limited, results indicated allergy as the major cause in 9 cases co-operating between 1/25 and ¼ year and in 8 cases between ¼ and ½ year.

Time when first improvement from anti-allergic therapy became evident:
Average of 10 days (2-30 days)

TABLE VI-B. RELATION BETWEEN CO-OPERATION AND RESULTS OF TREATMENT

Cooperation		Results of Treatment			
		Excellent	Good	Poor	Absent
Excellent	55%	45%	8%	0	2%
Good	30%	2%	24%	2%	2%
Poor	11%			9%	2%
Death (In first 2 weeks)	4%				

cooking vegetables, the previous ingestion of which had definitely increased her liquid stools.

A reduction in the stools, urgency, blood, fluidity, abdominal distress, and fever in one to three weeks favors food allergy. In our patients, initial improvement was noted in an average of ten days, this varying from one to thirty days. Since one to four weeks may be required before previously ingested foods leave the body and more time is required thereafter for the tissues to regain normality, increasing improvement often continues for two or more months. After relief is assured, other foods one by one can be tried, adding oatmeal, egg, beef, other vegetables, and finally wheat and fruits, eliminating any which cause symptoms. Because of the frequency of milk allergy, we do not add milk or its products for one to three years. When a history of aversion or idiosyncrasy occurs, milk is excluded for several years or indefinitely. The severe, prolonged recurrences after trial of milk in several of our patients are added deterrents to such additions.

These patients with food allergy need continued supervision and policing[9] to prevent even slight breaks in the diet or unadvised addition of foods which may produce slight and later increasing recurrences. Laboratory tests and weight and nutrition must be checked, and proctoscopy and x-ray of the colon must be done every one to two years. If relief does not increase or even occur in one month, allergy to foods in the diet or to inhalants, especially pollens, must be suspected.

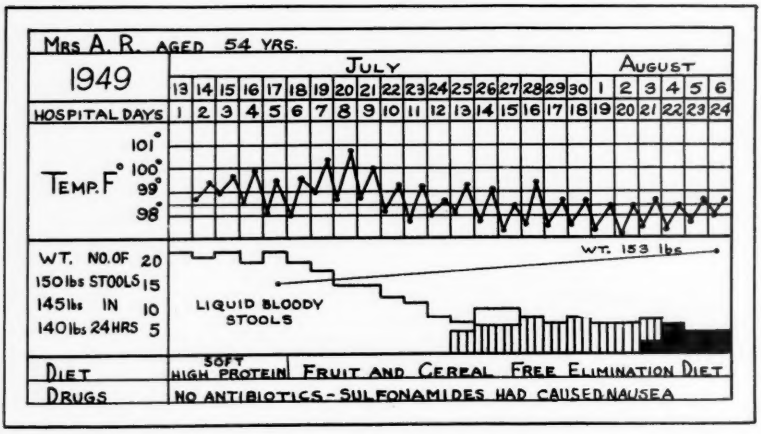
MRS A. R. AGED 54 YRS.
1949
JULY
AUGUST
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 1 2 3 4 5 6
HOSPITAL DAYS 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TEMP. F° 101° 100° 99° 98°
WT. NO. OF STOOLS
150 lbs
145 lbs
140 lbs
IN 24 HRS
20 15 10 5
WT. 153 lbs
LIQUID BLOODY STOOLS
DIET
SOFT HIGH PROTEIN
FRUIT AND CEREAL FREE ELIMINATION DIET
DRUGS
NO ANTIBIOTICS - SULFONAMIDES HAD CAUSED NAUSEA

Fig. 1. Case 2. Chronic ulcerative colitis for three and one-half months. Loss of forty pounds. Sulfonamides caused dermatitis. Penicillin increased diarrhea. Lifelong dislike for milk. Food allergy indicated by relief of diarrhea with the elimination diet with no drugs or antibiotics and continued control for four and one-half years with elimination of milk, egg, and fruit. Increase of weight in hospital has continued up to 185 pounds in 1954.

Space permits only the inclusion of three summarized cases with charts similar to those previously published.

Case 1.—A woman of twenty-seven years was first seen in March, 1952, because of chronic ulcerative colitis which had been present for nine years, associated with anal spasm and inflammation, for which two operations had been done. Soft, watery stools with blood, mucus, tenesmus, and some incontinency had continued, exaggerated with her periods. Suggesting allergy was nasal congestion, postnasal mucus, and aching in the upper teeth especially in the winters. Milk had constipated her in youth and increased her present colitis. Nasal and bronchial allergy were in the grandmother and son. Proctoscopy revealed erythema, easy bleeding, granulation, and edema of the mucosa. X-ray showed no haustrations and a feathery edge and abnormal mucosal pattern throughout the colon. Scratch testing with foods and inhalants was negative. No ova or parasites were found in the stools.

Treatment and Progress: To study food allergy, our minimal fruit-free elimination diet with C and B complex vitamins were given. In one week, two formed stools with no blood, mucus, or tenesmus resulted. Exaggeration at periods ceased. Since then all foods have been added except milk, fruits, and wheat, which have reproduced diarrhea.

Case 2.—A woman of fifty-four years was first seen in July, 1949, because of severe chronic ulcerative colitis which had been present for three and a half months. Sulfathalidine had caused fever and dermatitis, and penicillin had increased diarrhea. Weight had fallen forty pounds. Constipation had occurred for ten years, with mucus and traces of blood at times. Nausea, vomiting, and diarrhea had recurred two to three times a year all of her life, attributed to various foods.

Diet history revealed a long dislike for milk. Family history revealed sick headaches in her mother. Sigmoidoscopy showed a granular, erythematous, friable mucosa with small diffuse ulcerations. X-ray revealed chronic ulcerative colitis in the colon distal to the cecum. Ova and parasites were absent in the stools. Hemoglobin was 57 per cent. Other laboratory tests were negative.

Treatment and Progress: To study food allergy, our fruit- and cereal-free elimination diet was ordered, with no drugs or antibiotics. The relief of bloody diarrhea and slight fever is shown in Figure 1. Two transfusions were given. Although bismuth subcarbonate and Tannalbin were given, they probably were unnecessary because of their usual ineffectiveness in this disease. Nupercaine ointment caused allergic pruritus, disappearing after it was stopped for six weeks. In the last four and a half years no colitis has recurred except when milk, egg, and fruits have been taken. Bowels are normal and recurrent nausea and vomiting have been absent. She has gained forty pounds.

Case 3.—A man of thirty-eight first developed chronic ulcerative colitis in the spring of 1939. It was fulminating in two months, with a pustular dermatitis on the abdomen, an ischeorectal abscess, and a fatal prognosis. After gradual improvement, three to five soft or liquid, at times bloody, stools persisted. A severe fulminating attack recurred in the spring of 1941, with spreading dermatitis on the neck and feet. After our fruit-free elimination diet was started in July, stools and fever gradually became normal and eczema disappeared. Our experience suggests that the fever might have disappeared without the sulfaguanidine. In the last thirteen years, chronic ulcerative colitis has been absent except for fulminating attacks in 1942, 1945, and 1950 when forbidden milk, fruits, and condiments were eaten. Because of the severe colitis in 1939 and when first seen in the spring of 1941 and moderate recurrence in the springs of 1946 and 1947, pollen desensitization has been perennial, along with the strict elimination diet, in the last nine years. With this anti-allergic treatment and no drugs, he has been well, working in a factory daily, at times during the war for seven days a week and ten hours a day, since 1941 except for the symptoms in 1950. At present, fewer drugs would be used during fulminating attacks, as discussed in this article.

POLLEN ALLERGY

Pollen allergy alone is indicated by the recurrence of colitis, or when associated with food allergy by exaggeration of symptoms, during the pollen seasons. As shown in Table V, skin reactions may be large and numerous in a few patients or slight or absent in others. Positive reactions to pollens, moreover, occurred in eleven patients in whom pollen allergy was absent. The diagnosis has to be confirmed by good results from pollen therapy. Multiple antigens containing all important pollens in the patient's area are administered, usually starting with the first reacting dilution, determined with intradermal titrations, continuing with stronger dilutions as tolerated. In some patients very weak dilutions must be continued for one to two years, and maximum desensitization with the strongest dilutions may not be attained for three to five years. During the pollen seasons, an air filter, preferably with temperature control, may be helpful.

We have published three cases of seasonal chronic ulcerative colitis[9]

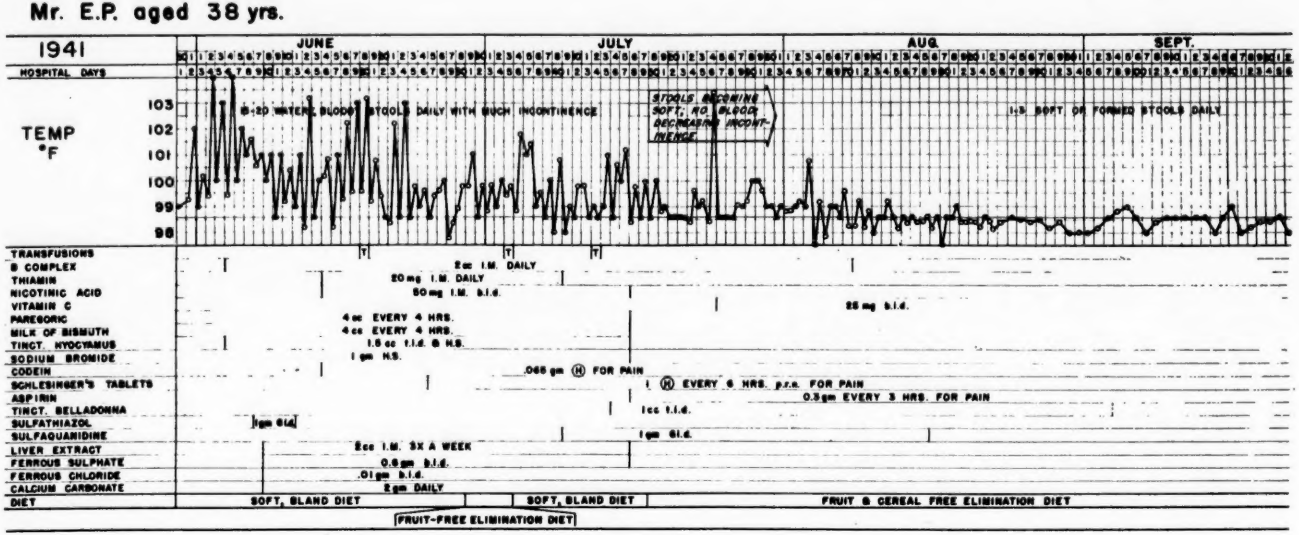

Fig. 2. Case 3. Fulminating ulcerative colitis with spreading pustular dermatitis in May and June, with a similar attack in 1939. This was controlled with the elimination diet and since then except for three attacks after breaks in the diet. Original attacks and moderate recurrence in 1946 and 1947 in the spring indicated pollen allergy and desensitization therapy. The sulfaguanidine given in the first hospitalization may not have been necessary since excellent results have continued for thirteen years with the diet and pollen desensitization and without drugs or antibiotics.

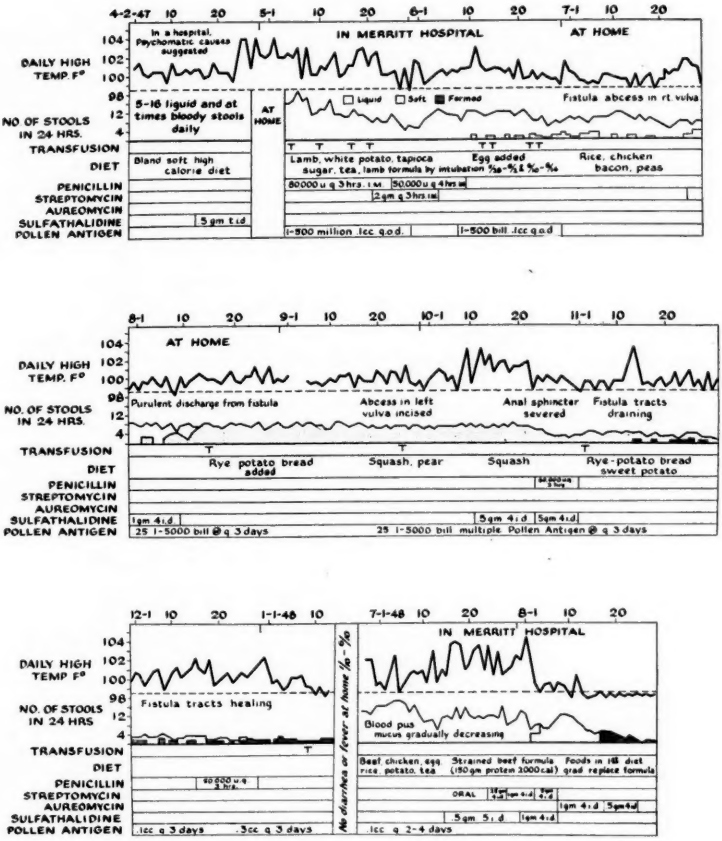

Fig. 3. Case 4. A girl of twelve years. Allergy to pollens, especially grasses, as the major cause of C.U.C. is indicated by its onset in July, 1946, relief in the winter and return of fulminating colitis March to mid-July, 1947, soft and decreasing stools with fever from infected fistulae in the fall, complete relief from January to June, 1948, and a lesser attack for one and one-half months in June and July with continued insufficient pollen therapy. Since then for five and one-half years, colitis has been entirely absent except for slight increase in the formed stools in the summers of 1949 and 1951.

which have been definitely relieved with pollen therapy alone. One has been entirely controlled with continuous treatment and no diet or drugs for thirteen years. Another with severe colitis in the summer and fall has been increasingly controlled with similar therapy for three years. In addition to the case summarized below, three other cases relieved with pollen therapy and aided by the elimination of possible allergenic foods are reported. In addition, other patients with evident or probable pollen

TABLE VII. GOOD OR EXCELLENT RESULTS

With anti-allergic therapy alone, with no antibiotics or drugs	47%
Patients also receiving sulfonamides	26%
Patients also receiving Azopyrine	22%
Patients also receiving antibiotics	13%
Patients also receiving cortisone or ACTH	12%

and food allergies have been treated. Two patients with chronic ulcerative colitis relieved by pollen therapy in the first and second years respectively have not been well controlled in the third and fourth years. One, under other medical care, has had a colectomy with definite benefit. This failure to satisfactorily control all patients does not disprove allergy as the major cause, since we cannot expect with present knowledge to get excellent results in all patients any more than in other manifestations of allergy, such as allergic asthma or dermatitis.

Allergy to house dust, animal emanations, fungi, or other inhalants was probable but not confirmed in one patient. It was slightly suspected in a few other patients. Bacterial allergy has not been confirmed in our work.

Case 4.—A girl of twelve years first developed chronic ulcerative colitis in July, 1946. It recurred in the spring of 1947, becoming fulminating with high fever and loss of about forty pounds in May when we first saw her. Although scratch reactions to inhalants were negative, pollen desensitization was started in a pollen-free hospital room. Food allergy was suggested by a long dislike for milk and eggs and was studied with a minimal fruit-free elimination diet. Because of anorexia and nausea, our strained meat formula[12] containing 100 grams of protein and 2,000 calories with synthetic vitamins was taken frequently by mouth and for a time by intubation. For probable infection, antibiotics were given. Stools decreased and became soft in the late summer and fall. Fever continued due to a recto-vaginal fistula. During the late winter and spring, formed stools and no fever occurred with pollen therapy, her elimination diet, and healing of the fistulae. A fulminating briefer attack recurred in June, 1948, due to inadequate pollen therapy. The fever was controlled apparently by aureomycin. During the last six years with continued pollen therapy, she has passed one to two formed daily stools, except for moderate colitis in the summer of 1949 and slight colitis in 1950. None has occurred in the last three years. All foods are now taken except milk, to which allergy may now be absent. She weighs 128 pounds and leads a normal social and student life.

ADJUNCTIVE THERAPY

When secondary infection is probable or present, antibiotics usually are advisable. Though less efficient, sulfonamides also may be tried. Of these, Azopyrine is most effective, although it has been disappointing in a number of our thirty-five patients who received it. It is probable that some of those who had these medicaments would have recovered with the anti-allergic therapy alone, with which good or excellent results did occur in 40 per cent of our cases. Some of these patients were relieved before antibiotics were available and before the new favored sulfonamides, especially Azopyrine, were made (Table VII).

TABLE VIII. RECURRENCES AND EXACERBATIONS

Number of: 45 in 38 patients	
Explained by breaks in diet	32
Explained by inadequate pollen therapy	12
Depression, refusal to eat, and infection (in 1945)	1

TABLE IX-A. ILEOSTOMIES

In co-operating patients since 1946	2
Previously advised but prevented by our anti-allergic therapy	13
Done in our patients before 1947	11
After stopping our beneficial therapy	6
After failure of our therapy before 1946	3
With no previous anti-allergic therapy	2
After failure of our therapy in 1949	1
After perforation from cortisone in 1953, previously well controlled by anti-allergic therapy	1

TABLE IX-B. DEATHS: NINE

None since 1946

After ileostomies	2
From peritonitis in first 2 weeks of treatment	4
From perforation and peritonitis after ileostomy following 3 months of therapy	1
Following ileostomies and colectomies after stopping our successful anti-allergic and adjunctive therapy	2

Cortisone and ACTH have been given to only seventeen patients, usually during the first weeks in fulminating cases and in small continued doses in only four patients. One patient who was well controlled with an elimination diet and was especially allergic to milk requested cortisone, hoping to increase tolerance for additional foods. Perforation of the sigmoid occurred in three weeks above a former stricture, the infection being controlled by terramycin. In one and a half years this area re-perforated and ileostomy was required even though the colitis had been and continued to be well controlled before surgery with her elimination diet. Cortisone in another well controlled patient led to perforation of a duodenal ulcer which had been inactive for twenty years. Previous reports of perforation also caution the use of these steroids and emphasize in our opinion the importance of anti-allergic control before or certainly in conjunction with such drugs. Sloan[18] and associates in 1951 reported perforation of duodenal ulcers from corticotropin given for ulcerative colitis. Palmer[7] and Kirsner[5] in 1951 reported perforation of the colon with corticotropin. Tulen[19] and associates in 1952 found perforations in the intestines in three patients with ulcerative colitis treated with corticotropin. Pessel[8] and associates in 1952 encountered a fatal case of multiple perforations of the colon and peritonitis while corticotropin was given for ulcerative colitis. Sauer[17] and associates in 1953 reported perforation and sloughing of the colon in one case of ulcerative colitis and perforation of the small bowel in two patients with regional enteritis treated with corticotropin or cortisone. Other complications from cortico-steroid therapy in additional gastrointestinal manifestations were reported in some of these contributions.

For anemia and hemorrhages, iron and transfusions are indicated. When the prothrombin is low, Vitamin K is necessary. Until good control occurs, possible benefit from parenteral B complex, B_{12}, and possibly non-specific therapy is advisable. For obstruction, threatened or actual perforation, and irreversible ulcerations and contractures, ileostomy and colectomy must be done. Conservative surgery on fistulae and abscesses is also necessary. However, with our anti-allergic and adjunctive treatment, only one ileostomy and colectomy for obstruction at the ileocecal valve and severe diffuse ulceration in the colon and the one ileostomy for perforation after cortisone (Table IXA) have been done in co-operating patients in the last eight years.[9] Two other ileostomies and colectomies were done for severe colitis probably due mainly to pollen allergy, for which in our opinion long-term pollen therapy might have prevented surgery, as in Case 4. Before 1947, twelve ileostomies with three colectomies had been done in nine years. Six of these patients had stopped our anti-allergic therapy which had been beneficial. Four patients had failed to respond to our control, which might have been successful today with our added experience and the present antibiotics and cortico-steroids. Two patients who died after ileostomy in 1942 and 1945 had no anti-allergic study or control. Moreover, the seven deaths before 1947 occurred from peritonitis which might have been prevented or controlled with present antibiotics and anti-allergic control. Two of these occurred after ileostomies done elsewhere after our previously beneficial therapy had been stopped. Since 1947 no co-operating patients have died. Of added interest were the ileostomies previously advised in thirteen patients which have been obviated with our anti-allergic, and in some of them adjunctive, therapy. Thus, with adequate and experienced study and control of allergy, it is our considered opinion that ileostomies and colectomies will decrease and the recently advocated ileostomy clubs will become less necessary.

RESULTS

With this consideration of food and pollen allergy in all patients, our results indicate that the ulcerative colitis was due to food allergy alone in 45 per cent, associated with pollen allergy in 10 per cent, with questionable pollen allergy in 15 per cent, due to pollen allergy alone in 3 per cent, to pollen allergy and food allergy in 10 per cent, and to pollen allergy and questionable food allergy in 9 per cent. Thus food allergy was indicated in 70 per cent and pollen allergy in 22 per cent. Questionable food allergy and questionable pollen allergy occurred in 7 per cent. Causes were not indicated in 8 per cent. Nine deaths occurred before 1947, as noted in Table IX B.

The relation between co-operation and results of treatment in Table VI show the importance of excellent co-operation. These results alone justify in our opinion the adequate study of atopic allergy in this disease.

The good results which occurred with good co-operation are noted. By good results is meant minimal soft or formed and at times liquid stools with occasional or no traces of blood, with intermittent or no cramping, and rare or no urgency. Occasional but usually slight breaks in the diet, inadequate pollen desensitization, and rare or questionable secondary infection were the apparent causes of these symptoms.

The infrequency of recurrences (Table VIII) in our patients, we opine, was mainly due to the control of the causative allergies and is in contrast to their greater frequency with other treatments,[3] especially when present steroid therapy is discontinued. We emphasize the importance of continued co-operation in anti-allergic therapy. In our cases the average was 3.7 years or a total supervision and study personally conducted by the writers of 488 years in 138 patients.

If a philosophy of acceptance of diet restrictions and advisable constant co-operation and the importance of prolonged pollen desensitization, which is also required in other manifestations of pollen allergy, such as hay fever, asthma, and atopic dermatitis, along with a greater understanding of the allergic nature of their disease had been obtained, we opine that more excellent results would have occurred. To accomplish this, the physician must perforce see or hear from the patient every week for several months after the initial control and then every few weeks or months and later two or three times a year. Our studies and results of treatment increasingly diminish the emotional and psychogenic influences to a secondary or minor role. Thus the marked apprehension and nervousness in the uncontrolled patient usually disappear as the symptoms are relieved. One patient with persisting and recurrently activated chronic ulcerative colitis had become increasingly nervous, discouraged, frustrated, and hysterical. As hospitalizations recurred, funds were exhausted, his job was lost, and dissension occurred at home. Hysteria and mania led to commitment to an asylum, from which he was released in two months when he rapidly accepted his invalidism. In one month with our anti-allergic therapy, with no medications, his colitis and nervousness were controlled. In the last eight months his bowels and psyche have been normal. He has worked steadily as a bill collector, and his weight has increased twenty pounds and he feels better and more relaxed than in many years.

REGIONAL ENTERITIS

Atopic allergy in our opinion also best explains regional enteritis.[13] The characteristics and symptoms, with the gross and microscopic findings, favoring allergy have already been summarized. Eosinophilic tissue infiltration reported recently in America[4,13] and for many years in Europe[13] especially suggests allergy. The occurrence of ileitis in 11 per cent of our patients with chronic ulcerative colitis suggests the same cause for both diseases in the large and small bowel. The relief in patients with our

elimination diets favors food allergy. The history of exaggeration or occurrence of symptoms in the pollen seasons, with or without positive reactions to pollens and with or without other manifestations of pollinosis indicates pollen allergy as a sole cause or associated with other allergy, especially to foods. Such pollen allergy, suspected in several patients, has not been confirmed, however, by the results of therapy because of failure of adequate co-operation. One patient with ileo-colitis for nine years had increasing diarrhea, abdominal cramping, tenesmus, loss of weight, episodes of fever, and fibrositis in the feet and legs for nine years. These symptoms arose after an appendectomy. An increasing obstruction for an advancing granuloma in the right lower quadrant had necessitated an ileo-transverse colostomy four years before we saw her. Because of exaggeration of symptoms in recent years during the pollen seasons, even though skin reactions to pollens were negative, pollen desensitization was started and was continued for two and one-half years with excellent control of all symptoms during the last two years. Her former semi-smooth but ineffectual diet, with multiple vitamins and no drugs, has been continued.

Our experience indicates food allergy as the common cause of regional enteritis. Our published case[13] of continued diarrhea and varying constant fever for eight years, not benefited by removal of two feet of the terminal ileum in which marked eosinophilic infiltration was present, has received entire relief for five years with a milk-free diet alone, with no medications. The initial typical x-ray findings of dilatations, contractures, and abnormal mucosa in the jejunum and especially in the ileum has gradually resolved to practical normality with this milk-free diet.

A man of thirty-five years developed two to six watery stools in 1947, with no previous gastrointestinal symptoms. Diets and drugs were ineffectual. During 1950, severe pain also recurred every one to two months. Regional enteritis was diagnosed, and a transverse colectomy was done, using ileum twelve feet from the cecum because of skip areas up to and even above that level. In the last three years, soft and, up to eight months, watery stools had continued, with increasing abdominal distress. Laboratory tests, including stool studies for ova and parasites and scratch testing with inhalants and foods, were negative. With a minimal fruit-free elimination diet plus egg and oatmeal, diarrhea decreased in three weeks, and for four months two to four soft stools sometimes formed and sometimes liquid, have occurred, and cramping has ceased. Other foods will gradually be added, eliminating those which produce diarrhea. The patient is reconciled to a restricted diet which has increased weight by eight pounds and has increased his energy. We hope that with continued control of the probable food allergy that his intestinal inflammation will subside or disappear as it has in the above summarized case.

The anti-allergic study and control and adjunctive therapy as advised

above in chronic ulcerative colitis are also used in our cases of regional enteritis.

SUMMARY

1. For sixteen years our studies and therapy increasingly indicate that atopic allergy to foods and/or pollens and rarely to drugs is responsible for chronic ulcerative colitis and regional enteritis, causing an eczematous-like allergic inflammation.

2. The localization, spreading tendency, remissions, and exacerbations occur in other manifestations of allergy, especially atopic dermatitis.

3. The gross and histologic tissue changes, causing the erythema, granulation, friability, round cell infiltration with eosinophiles in regional enteritis, the thromboses, necroses, ulcerations, and perforations are best explained by allergy, at times with secondary infection.

4. When allergy is the sole cause, anti-allergic therapy alone controls the symptoms. When secondary infection, anemia, and avitaminosis are present, their control also is required.

5. Analysis of the histories, laboratory studies, and results of anti-allergic and indicated conjunctive therapy of 138 cases of ulcerative colitis are presented.

6. Results indicated causative food allergy alone in 45 per cent, pollen allergy alone in 3 per cent, indicated or questionable food and pollen allergies in an additional 25 per cent for foods and 18 per cent for pollens.

7. Food allergy was studied and controlled with our fruit-free elimination diet plus rice, modified as advised, or with our minimal fruit-free elimination diet. Strained meats or our strained meat formula were utilized in severe or fulminating cases. Although any food may be responsible, milk especially and often fruits, chocolate, condiments, at times legumes, beef, fish, and specific vegetables were responsible. With gradual relief, individual foods were added carefully as advised.

8. Pollen allergy requires prolonged desensitization with multiple antigens and at times pollen filters and environmental control. Skin reactions at times are negative.

9. Adjunctive treatment for secondary infection, anemia, and avitaminosis is discussed. Indications for and complications of ACTH and cortisone are summarized.

10. With anti-allergic therapy, with or without adjunctive treatment, excellent results were obtained in 45 per cent and good results in 8 per cent with excellent co-operation and excellent results in 2 per cent and good results in 24 per cent with good co-operation. In the last eight years, there have been no deaths in comparison with nine in the previous eight years. Only two ileostomies and colectomies have been done in eight years in co-operating patients. Present antibiotics and increased experience in anti-allergic treatment best explain these results.

11. In the sixteen years of our treatment, there have only been thirty-

eight exacerbations, compared with the greater reported number with other therapies.

12. Our study and treatment of regional enteritis indicate those causes responsible for ulcerative colitis. Two cases in which food allergy is the indicated sole cause are summarized. Cases with seasonal symptoms suggesting pollen allergy have refused co-operation in desensitization therapy.

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CLIMATE AS AN INFLUENCING FACTOR IN CHILDHOOD ALLERGY

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CLIMATE as an influencing factor in childhood allergy represents a problem with many controversial aspects. The opinions are so varied as to render this subject of considerable interest and importance. My own interest in the problem originated eighteen years ago after settling in southeastern Florida. Here I frequently encountered many children who were brought to the area from other parts of the country for relief from allergic symptoms. Like others unfamiliar with the relation of climate to allergy, I ventured the opinion that a more or less uniformly warm, sunny climate like that in southeastern Florida should aid the allergic child. As my experience increased, however, I found that this proved true in only a relatively small percentage of patients. In the others, either the allergic symptoms remained the same or became more severe because of newly created etiologic factors.

Although primarily interested in the effect of local (Florida) climate on childhood allergy, no presentation of this type would be complete without first briefly reviewing the influence of climate in general on allergic children, i.e., the climate in other parts of the country. As the time factor mitigates against a detailed discussion, only the highlights will be presented. The facts to be given are based on (1) a review of the literature; (2) the response to a questionnaire sent broadcast to allergists and pediatricians; and finally (3) my own personal experience.

REVIEW OF THE LITERATURE

Since it is occasionally deemed desirable for physicians to recommend that patients with intractable allergy migrate to other areas for relief of their symptoms, it is of no small moment to know whether such a step is of therapeutic value. That the results are often disappointing has been pointed out. In an editorial[3] in the *Journal American Medical Association* this fact was stressed with the qualifying statement that although some migrant patients are improved, they are few compared with those that are either not improved or made worse. It was brought out further: "Careful analysis of the case records of those who are apparently cured by migration reveals that the real cause of the cure in many patients was the concurrent application of some recognized measure such as removal from pets, which could have been accomplished at home."

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Schutzbank[10] analyzed 150 patients who came to Tucson, Arizona, for relief of allergic disorders. Seventy-two per cent were benefited, and 28 per cent were not helped. Of 101 asthmatic persons seventy-four were benefited from 50 per cent to complete relief of symptoms. It is interesting to note that eleven patients experienced hay fever for the first time, and eight had more severe hay fever than they had had before coming to Tucson. Fifteen patients who formerly had hay fever had no symptoms of pollinosis in Arizona.

Criep and Hammond[2] wrote on the regional factors in allergy, introducing their paper with the statement that environmental factors, as is well known, affect the incidence, frequency, and severity of allergic diseases. This report was based on geographic factors influencing the climate in the area embracing western Pennsylvania and the adjacent portions of West Virginia and part of Ohio, with Pittsburgh as a center.

In this Pittsburgh area, Criep and Hammond observed that patients are better in the summer than in the winter, provided they are not sensitive to pollen. Factors other than temperature contribute, however, to this end result. Specifically, these are the prevalence of respiratory infections in the winter, and exposure to fumes, gas heat, and indoor dust because of confinement to the house. Criep and Hammond concluded that climatotherapy is of unquestionable value in carefully selected patients.

Rowe[9] called attention to the seasonal and geographic influences of food allergy, especially in northern California and in the San Francisco Bay area. He noted that (1) these effects may both occur in varying degrees in the same patient or either one may act alone without any evident effect of the other; (2) all food-sensitive patients are not affected by these influences. Those with chronic food allergy, especially with bronchial and to a lesser degree nasal allergy, are most susceptible.

As concerns hay fever, Peshkin[8] stated: "The severity of hay fever during any particular season varies with the pollen content of the air, which depends upon rainfall, sunshine, humidity and wind. Sunshine increases pollen production. Rainfall, especially a slow rain over several days, practically entirely frees the air from pollen. Sustained drought reduces the pollen crop. It has been shown that as the humidity rises the symptom curve falls. High wind velocity increases the pollen content of the air and carries it to greater distances." According to Peshkin, climate has a marked influence on the growth of vegetation, certain pollen-producing plants growing well in one area and sparsely or not at all in another.

Harsh[5] emphasized that there is a direct correlation between humidity and house dust sensitivity. He concluded that patients with a high degree of sensitivity to house dust will probably not obtain relief by going to a humid climate. He believed that the greater incidence of respiratory allergy in a humid climate is not due to the climate *per se* but to the humidity rendering house dust more allergenic.

Feinberg[4] asserted that climate may affect respiratory allergy in that

the changed environment may have less of the airborne substances which cause the allergy. In his experience, children seemed to do much better as a result of climatic change than adults.

FLORIDA CLIMATE AND CHILDHOOD ALLERGY

With full knowledge that the foregoing review is incomplete, it was necessary, as you know, to restrict it because of the time limitation for this paper and because I wish to include also some brief remarks on the influence of Florida climate on childhood allergy.

One of the pioneering reports on the latter problem was made by Metzger,[6] who reasoned that the subtropical setting of our state invites countless sufferers from all walks of life to seek climatic relief from hay fever and asthma. He classified those who come to the state for this purpose into three groups: (1) those who obtain no relief; (2) those who become worse in the new climate and environment; and (3) those who obtain complete or partial relief.

Metzger warned against taking up residence in Florida until all the essential facts pertaining to the patient's personal requirements, and especially his sensitivities, are well known. This is especially true of the house dust-sensitive patient who, he thought, would not do well in this climate. It is generally conceded, and Metzger has stressed, that the east coast section affords freedom from symptoms to all sufferers from the pollen of ragweed; the midstate section and the west coast are suited to all except those highly sensitized to this pollen. In selected cases in which nonspecific causes are of importance, Metzger believed that the climate of Florida may be of particular benefit, but that despite this, the problem of the allergic patient must be individualized.

Zivitz[11] studied the effect of the Miami (Florida) climate on imported allergic problems, and, like other workers, noted that some patients obtained varying degrees of relief while others were not benefited at all. He expressed the view that only under the following conditions would climatotherapy in the Miami area be considered indicated: (1) When careful and complete studies have failed to relieve the patient; (2) when the patient is benefited mostly or entirely by atmospheric conditions created by modern methods of humidity and temperature control to simulate Miami. Under certain circumstances, however, the local climate should be considered an adjunct method of treatment.

An allergy survey of Florida was made by Bernstein and Klotz,[1] who broke down the pollen findings by regions into the northern, middle, and southern zones. It was revealed by these workers that South Florida has practically no ragweed, some Australian pine and grass pollens, and appreciable quantities of molds. Mid-Florida has less mold, slightly more grass and appreciably larger amounts of ragweed pollen. The North Florida zone is more like the southeastern United States, slightly more ragweed and a heavier tree season, notably pecan. In Bernstein and

Klotz's opinion, Florida is a good area for victims of allergy, not only because of the low pollen counts, but because of the reduced temperature ranges over the state, both as between seasonal extremes and from day to day, likewise from indoors to outdoors throughout the year.

An aerobiologic survey of the Miami Beach district performed by Palay[7] disclosed: (1) Grass pollen is insignificant; (2) Ragweed pollen is scarce and almost completely absent during August, September, and October, making this district a perfect haven for ragweed patients; (3) Australian pine has a definite pollinating season and produces a large quantity of pollen; (4) For some air-borne molds there is a "season" which is reflected in patients' symptoms, but for others this is not indicated.

RESPONSE TO QUESTIONNAIRE

Since I wish to present an unbiased point of view concerning both the general influence of climate and the more specific influence of Florida climate on childhood allergy, questionnaires were sent out to pediatricians and allergists in various parts of the country. One hundred questionnaires were sent out in the state of Florida with 70 per cent response. The questionnaire posed the following questions:

1. How many children do you see during the year who were allergic up North in their former residence and have come to Florida to live?
2. Has it been your observation that a percentage of these children has improved by change of residence to the Florida area?
3. Have children who have not been allergic up North developed allergy by change of residence to the Florida area?
4. In your opinion, in a general way, is the Florida area conducive to improvement or complete cure of certain allergic conditions in children?
5. What is your personal opinion as to the relationship of climate to allergy, especially in children?

The questionnaires sent to non-Floridian specialists brought out the following facts:

1. There is a distinct division of opinion concerning the therapeutic value of climate in allergy in general, and childhood allergy in particular.
2. Climate may effect respiratory allergy in that the changed environment may contain less of the air-borne substances which cause allergy.
3. Frequent incidence of upper respiratory tract infections seriously interferes with specific immune therapy, and changes to a warmer climate break the allergic cycle.

One answer was especially noteworthy, holding that climatic change as a treatment for allergy in children was nothing more than an escape and was rarely necessary if indicated conventional management was carried out.

The following generalizations can be made from the answers to the questionnaires sent to Floridian pediatricians and allergists:

1. Most allergic children who came here improved up to a point, but the degree of improvement depended on the type of existing allergy.

2. In some instances the improvement was permanent; in others, only temporary.

3. The critical period of change was generally considered to be two to three years. In other words, if relapse did not occur after this period of residence in Florida, further improvement in the respiratory allergic condition could well be anticipated.

4. Many children, though non-allergic in Northern climate, developed respiratory allergic symptoms by migration of the family to Florida.

The consensus seemed to be that if South Florida favored improvement it was largely because its climate reduced the incidence of upper respiratory tract infections and afforded freedom from Northern pollinosis.

GENERAL COMMENT AND PERSONAL EXPERIENCE

Climate is a peculiar phenomenon, and the peculiarity becomes especially manifest when one endeavors to determine its influence on allergy. The multitudinous factors embraced in the definition of climate—temperature, moisture, et cetera, render it difficult to state which of the factors frequently accounts for the variation in allergic symptoms. In the basic sense, childhood allergy does not differ from adult allergy, though habits, occupation and physical factors incident to age have to be considered in evaluating influences.

My personal experience coincides with the answers given in the questionnaire. It is my firm conviction that the child with allergy may benefit from the climate in southeastern Florida if all other means have been exhausted in his former place of residence. However, it is my further conviction that Florida is no place for the "trial and error" method of therapy. Every allergic child is entitled to a careful allergic workup and adequate indicated management before being sent to this area. Only after failure by recognized and accepted therapeutic methods should the possible advantages of a uniformly warm climate be considered. The pediatrician or allergist should know, however, if the particular area he recommends promises freedom from existing offenders; otherwise, failure rather than success will be the rule.

In studying and treating allergic children in southeastern Florida, I have found house dust the all-important inhalant allergen. Dust collected from homes in this area and extracted in the usual manner is less potent therapeutically than the extracts prepared according to the method of Boatner and Efron,* but in some patients autogenous house dust extracts have proved effective. Harsh's[6] supposition that humidity renders house dust more allergenic by bacterial decomposition is thought-provoking.

Contrary to the observations of other workers, I have not been convinced that molds in southeastern Florida are of unusual significance as an etiologic factor in childhood allergy. In my opinion they rank secondary to house dust as an offending allergen.

*Endo Products Co., Richmond Hill, N. Y.

As a final word, I should like to stress that every child must be managed on an individual basis—individualizing every possible aspect of the problem from cause to therapy, not omitting the psychogenic factors that may be involved. From historic times climate has always been regarded as a valuable therapeutic agent. It is still a weapon of considerable virtue whose potentialities in allergy remain to be explored further.

SUMMARY

Climate as an influencing factor in childhood allergy represents a problem with many controversial aspects.

In a general way, though some migrant allergic patients are improved, they are few compared with those who are either not improved or made worse.

It has been shown that there is a direct correlation between humidity and house dust sensitivity.

As concerns respiratory allergy, climate may affect it in that the changed environment may have less of the air-borne substances which cause allergy.

To ascertain the opinions of other workers throughout the state of Florida on the influence of its climate on allergic children, a questionnaire study was carried out.

The consensus pertaining to South Florida was that if its climate favored improvement, it was largely because of the reduced incidence of upper respiratory tract infections.

House dust is the most prominent inhalant allergen in southeastern Florida, but dust collected from its homes and extracted in the usual manner is less potent than the extracts prepared according to the method of Boatner and Efron.

In the final analysis, irrespective of all factors, climate included, every allergic child must be managed on an individual basis.

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TREATMENT OF THE RHEUMATIC DISEASES BY DESENSITIZATION WITH AN AQUEOUS EXTRACT OF STREPTOCOCCI

III. Rheumatoid Arthritis

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RHEUMATOID arthritis is perhaps recognized in its earliest stages less frequently than most diseases because the lesions of the joints are not prominent in the beginnings of the disease. The patient, during a prolonged period of overwork and perhaps of emotional stress, presents physical tiredness to the point of exhaustion, loss of weight, and anemia as the earliest symptoms. Generalized soreness of the muscles usually precedes the first distinctive swelling, tenderness, and stiffness of the joints. Symmetrical involvements of the small joints of the hands are usually seen first. Once in evidence, the inflammation of these joints persists over long periods of time in contrast with those of rheumatic fever or gout in which the first involvements clear up completely. The joints later so dominate the symptom complex that the physician may overlook the general symptoms in his concern to influence favorably the great handicap of inflamed or deformed joints. The evolution of the diseased joints in rheumatoid arthritis is so well known that the end results in untreated cases are predictable. Progressive destruction of joint function rightly should be of great concern to the physician. Much may be done to lessen or prevent the graver deformities, but the local treatment of one or more large joints by measures which provide spectacular temporary relief is eventually likely to do more harm than good since it retards healing by encouraging their excessive use.

BASIC VS. SPECIAL TREATMENTS.

Patience is the essence of success in the treatment of rheumatoid arthritis. It is the most difficult of the rheumatic diseases to treat because there are so many basic considerations which must receive scrupulous attention on the part of the physician (Patient 2, Table I). His immediate concern should be that of relieving pain and distress. Experience teaches him to anticipate deformities and to institute measures to prevent them. Correction of posture and of contracture deformities already present must be undertaken. The need for management of diet, control of anemia and vitamin deficiencies is ever present. Physiotherapy applied for a definite purpose should not be allowed to overtax the patient's strength. A proper balance between rest and exercise should be adapted to each patient. Major surgery for the elimination of focal infection should be avoided because it so frequently adds to the debility of the patient.

An intelligent attitude in the use of special treatments is obligatory. Their use does not eliminate the need for rigid adherence to the basic general measures. In a chronic disease which is lifelong, the relief of symptoms by means of habit-forming or toxic drugs is contraindicated. Salicylate in moderate dosage usually provides considerable relief especially when combined with mild sedation. Its use does not interfere with other forms of treatment with which it may be combined. It may be used safely over long periods of time. Cortisone, corticotropin, and hydrocortisone are potent agents in eliminating pain and in improving general body tone but of doubtful value in promoting healing within the joints. The distressing deformities of the hands, for example, are not prevented by their use. A great practical consideration consists in their enabling a patient to continue at gainful employment which otherwise might be impossible.

We will present in this paper our treatment of rheumatoid arthritis by a desensitizing technique using subcutaneous injections of an aqueous extract of streptococci (AES).*[1] This method has been developed over a period of years. We now use it routinely. It should be regarded as a special form of treatment to be used in conjunction with the basic measures mentioned above. This treatment provides a means of controlling rheumatoid arthritis to the extent that uninterrupted employment over long periods is possible. (Patient 1, Figs. 1, 2, and 3). There are no contraindications. The only undesirable side-effects arise as slight aggravations of the arthritic symptoms when overdosage of AES has been used. These symptoms are easily recognized, and subside promptly following the adjustment of dosage downward.

CASE REPORTS

Patient 1.—T. S., a white man, forty-four years old, was first seen on September 17, 1928. He presented a rheumatoid arthritis of eight years standing with swelling, tenderness and limitation of motion in both wrists, both knees and the right elbow. He was given subcutaneous injections of the aqueous extract of streptococci (AES) at weekly intervals for nineteen weeks and four more injections at intervals of two weeks. He improved and discontinued treatment in April, 1929. He returned in June, 1934, more than five years later. He stated that he had not been troubled with his joints until March, 1934, or about three months previously, when following a heavy and persistent cold, he began to notice general soreness and stiffness, swellings of the right wrist, the right elbow, and both knees. The examination showed swellings of both elbows, both wrists, the proximal digital joints, and several of the metacarpophalangeal joints. There was atrophy of the interosseus muscles of the hands. Both knees were stiff, swollen and painful on weight bearing. The muscles of the thighs were flabby. He had difficulty arising from a chair and in walking. He was given injections of AES at weekly intervals for six weeks, and then at progressively longer intervals until intervals of five weeks became the routine. This was continued thereafter, until his death from an unrelated condition in October, 1952. During this entire period of twenty-four years he conducted an active central city retail business and was free of acute exacerbations. His latest

*The method of preparing this extract has been presented in another paper of this series.

Fig. 1. Showing complete flexion of the knees in Patient 1. Photographed January 21, 1950.

Fig. 2. *(above)* Hands of Patient 1. Photographed January 21, 1950.

Fig. 3. *(below)* Clenched hands of Patient 1. Photographed January 21, 1950.

condition showed normal clenching of the hands, freedom of movements in the elbows and wrists, and painless complete flexion of the knees. He could arise easily from a chair and walk without impairment. From time to time throughout the years, sedimentation tests of erythrocytes were made. Since January, 1935, the results of thirty such tests are in our records. Seventeen of them showed readings below 20 mm in one hour, and the highest reading has been 57 mm. This record is given to show the prolonged control of rheumatoid arthritis by perennial treatment with AES without detriment to the patient's general health.

Patient 2.—Mrs. O. A., a white woman, forty-six years old, was first examined on June 27, 1949. She complained of pain, swelling and stiffness in multiple joints including, as most acute at this time, those of the right hand, both feet, and the right wrist. Her illness began about two years previously with pain and swellings of the metacarpophalangeal joints and pain in the right shoulder. Stiffness and soreness in both feet began soon afterwards. For several months prior to the onset, she had been losing sleep in caring for her ill husband.

Physical examination: The patient was a pallid white woman, 68 inches tall and weighing 149 pounds. The pulse, temperature, respirations and blood pressure were normal. Examination of the pharynx, nose, sinuses and ears revealed nothing noteworthy. The cardiac sounds were of good quality. Normal findings appeared over the lung areas, and over the abdomen.

The proximal digital joints of the first and second fingers of each hand were swollen, tender, and painful upon limited motion. The first and second metacarpophalangeal joints of each hand were similarly involved. The right wrist showed a contracture and could not be moved without acute pain. It was swollen over the dorsal aspect but not acutely tender. There was bilateral atrophy of the interosseus muscles of the hands. The knees could not be flexed completely without pain but did not appear swollen. There was acute tenderness over each second metatarsophalangeal joint.

TABLE I. DETAILS OF TREATMENT

Dates and Intervals	AES Doses	Sed. rbc.	Remarks
		mm	Weight 149 lbs.
6-27-49	.1016*	62	Much improvement. Less swelling, tenderness, and pain.
to	.1016	—	
7-26-49	.2516	28	
5 injections	.2516	—	
7-day intervals	.1015	—	
7-26-49	.1014 X 3	55	Weight 150 lbs.
to	.2514		8-26-49. Continues to improve; not tired; doing own housework.
6-1-51	.1516	21	
	.1016	31	
48 injections.	.1015 X 3	30	
14-day intervals.	.2515		
	.1014 X 2		
	.1015		Weight 153 lbs.
2-1-50	.1012 X 2		Dosage increased too fast. Transient pain in knees, ankles, wrist, hands.
	.1013		
	.1012 X 2		
4-25-50	.2013	92	Weight 151 lbs.
	.1513		Improvement followed. Reduction of AES dosage.
	.2513	80	
6-6-50	.3513 X 12	78, 60	Weight 150 lbs.
	.0512		
	.1012 X 4	54	
	.2012	22	
	.1012		
	.2012 X 6		
	.2512 X 2		
6-1-51	.2512 X 8	16, 24.	Weight 156 lbs.
to	.3512		Has continued to do well during this period of more than two years.
9-17-53	.0511 X 5	38	
	.0711 X 2	30	
40 injections	.0511 X 2	31, 30	
21-day intervals.	.1211 X 4	45, 35, 23.	
	.2011 X 5	20, 23, 40.	
	.3211 X 6	12, 31, 15, 43.	Weight 159 lbs.
	.5211 X 8	51, 32, 40, 27, 39	
9-17-53	.0810 X 4	21	Continues to do well.
to			
1-7-54			
4i njections.			Weight 162 lbs.
28-day intervals.			

*In this and the other tables in this article, the first two digits indicate the volume dose in decimal part of a cubic centimeter, and the last two digits indicate the dilution of AES. When doses are repeated, this is indicated by "X" followed by the digit representing the number of repetitions.

Laboratory findings: Hemoglobin 80 per cent; erythrocytes 4,200,000; leukocytes 8,500 per cubic millimeter. Sedimentation of erythrocytes was 62 mm in one hour. Urea nitrogen 12 mgms; uric acid 2.8 mgms; and sugar 100 mgms per 100 cc of blood. The Kahn test was negative. The urine test was normal.

Diagnosis: Rheumatoid arthritis.

She was continued on a polyvitamin capsule, iron medication and on acetylsalicylic acid as required for pain. A generous diet was prescribed. She was instructed in certain corrective measures to aid in straightening the right wrist. In anticipation of the dreaded ulnar deviation deformity of the fingers, exercises were prescribed to develop the extensor and abductor muscles of the hands. Subcutaneous injections of AES were begun. In Table I are some of the details of this treatment as applied over a period of four and one-half years.

During the week following the first injection, the swelling decreased markedly in the fingers and right wrist. She was able on July 5, 1949 to move the wrist through an angle of 20 degrees and some of this motion was in extension. There was little tenderness about any of the involved joints after this date. Following the treatment of July 19, the patient developed generalized itching and transient pains in the ankles. The itching persisted until early October and, on the second and third days

TABLE II. RECORD OF TREATMENT

Dates	Intervals in Days	AES Doses	Sed. rbc. mm in 1 Hr.	Condition
1-16-53	0	.0517	91	See phys. exam.
1-20	4	.0517		Worse; more soreness in hands, shoulders, neck.
1-24	4	.0517		Same as above.
1-30	6	.0517		Same as above.
2- 6	7	.0517	82	Pain in hands; shoulders, neck better.
2-13	7	.1017	70	Better; two better days.
2-20	7	.0517	78	Pain at night; wakeful.
2-27	7	.0517	49	Much better; soreness in hands.
3- 6	7	.0517		Very much better.
3-16	10	.0817	41	Continues much better.
3-26	10	.1217	38	Good entire ten days; less swelling hands.
4- 9	14	.2017		Very well; slight stiffness in fingers.
4-29	20	.3217	20	Very well; delayed visit.
5-13	14	.1416	76	Very well; slight dizziness.
5-27	14	.6016	46	Very well; hands, wrists, shoulders free.

following an injection, a few urticarial lesions would usually appear. The dosage reduction on October 6, was followed by the disappearance of this condition of the skin as well as by a reduction of the resting stiffness. The improvement appeared in this patient more promptly than is usual. In general it was maintained. From February 1, 1950 to June 6, 1950 the doses were increased rather rapidly because they did not appear to be followed by a full fourteen days of relief. A relapse of symptoms would appear about the twelfth day. Increases in the doses were made in an effort to lengthen this period but these began to be followed by an excitation of the arthritic symptoms within the first twenty-four hours. These symptoms were mild and transient but during this period the sedimentation tests showed elevated readings. A stabilization of dosage was effected after June 6, 1950 and no further difficulty was encountered. This incident is emphasized because such incidents may lead to failure if not corrected. The progression of doses after June 1, 1951 follows the constant percentage increment progression presented in another publication.[2] We especially want to direct attention to the number of times a dose is repeated before advancing to the next larger one.

Patient 3.—Mrs. M. L., a housewife, fifty-eight years old, had some pain and stiffness in the hands and shoulders for about a year. During the past three weeks, the pain became much worse and she has noted swelling of the fingers. Pain has kept her awake at night. She has needed assistance in dressing in the morning because of soreness in the hands. There had been no recent acute illness.

Physical examination: The patient was a pallid white woman presenting swollen stiff hands which she guarded carefully. She was 64 inches tall and weighed 128 pounds. The tonsils were intact. Only three teeth remained. There was a soft systolic murmur at the cardiac apex and another over the base of the heart. The temperature was 98.0° F., and the pulse regular at 84 per minute. All of the proximal digital joints were swollen and presented fusiform appearances. The first and second metacarpophalangeal joints were swollen. All of these small joints were tender and painful. Both wrists were swollen, tender and restricted in movements. There was moderate atrophy of the interosseus muscles. The elbows and shoulders were stiff and painful upon restricted movements. The joints of the lower extremities were not involved.

Laboratory findings: 63 per cent hemoglobin; erythrocytes 4,000,000; leukocytes 10,800; and sedimentation of erythrocytes 91 mm in one hour were noted.

Diagnosis: Early rheumatoid arthritis.

Treatment: Mild sedation, salicylates and liberal amounts of ascorbic acid were advised. A liberal, well balanced diet and hematinics were prescribed. Rest,

TABLE III. RECORD OF TREATMENT

Date	AES Dosage	Sed. rbc. mm in 1 Hr.	Weight Lbs.	Condition
10-16-53	.1018	42	136	See history.
10-22	.1018 X 2	42	140	Unchanged.
10-29	.1618 X 2	32	140	Soreness rt. wrist. Better; less swelling.
11- 4	.1618 X 2	—	138	Extra stiffness in hands.
11-12	.1618 X 2	41	143	Very good period; Swelling gone.
11-19	.2618 X 2	—	142	Continues to do well.
11-25	.2618 X 2	—	141	Continues to do well.
12- 3	.4718	37	140	Continues to do well.
12-10	.1017 X 2	62	140	Continues to do well.
12-18	.1817	—	139	Slight reaction; Stiffness.
12-23	.2917	43	139	Stiffness.
12-29	.4717	43	139	Better; no stiffness in morning.
1-7-54	.7617	42	141	Reaction with swelling rt. wrist.
1-14	.1216	49	144	More soreness in wrists for four days.

stretching exercises and contrast baths for the hands were begun. The desensitization regimen with the aqueous extract of streptococci (AES) was started. The record of the earlier months of this treatment is presented in Table II. The first two weeks were discouraging in that all symptoms became worse. The initial very small doses of AES were continued for five injections. A larger dose was then tried, but when the pain at night became worse, we went back to the smaller dose. It was not until about five weeks after treatment was started that pronounced clinical improvement appeared. This was also reflected in the sedimentation tests. Once started the improvement quickly progressed to such relief that the patient became irregular in her visits to the office, and soon discontinued them. Her latest visit was on November 3, 1953 after an absence of two and a half months.

She had no complaints of pain nor stiffness. There was no swelling about the hands or wrists. Her weight was 131 pounds; hemoglobin 80 per cent; and the sedimentation of erythrocytes 55 mm in one hour.

Based on former experience this patient's arthritis may be expected to become active within four to six months after the injections were discontinued. The perennial plan of treatment with one injection of AES per month appears to be an assurance against such relapses.

Patient 4.—J. A., a twenty-nine-year-old nun, began to have pain, swelling and tenderness in the hands and feet three and one-half years previously. During the past year the hands and the wrists became more swollen and painful.

Physical examination: The patient was a white woman, 67 inches tall and weighing 136 pounds. The pulse was regular at 84 per minute and the blood pressure 104 systolic and 60 diastolic. The temperature was 99.0 F. There were no signs of infections about the ears, nose, sinuses, teeth nor pharynx. A soft systolic murmur was noted at the cardiac apex. No other noteworthy findings appeared upon examination of the chest or abdomen. The proximal digital joints of the first and second fingers of each hand, of the fourth finger of the left hand, and the first and second metacarpophalangeal joints of both hands were swollen. Both wrists were swollen and limited in movements. The first metatarsophalangeal joints of both feet were enlarged and tender. The hemoglobin reading was 70 grams per cent; erythrocytes 3,800,000; leukocytes 8,000; and sedimentation of erythrocytes 42 mm in one hour.

Injections of AES were started simultaneously with establishing the patient on basic treatment. Two injections per week were given. (Table III). This represents a departure from the usual procedure of one injection each week. It is being tested for its effects upon the latent period between the beginning of treatment and the onset of pronounced improvement of the arthritis. The swellings about the fingers began to decrease during the first week but only after three weeks was a reversal

of the arthritic process very definitely established. The readings of the sedimentation of erythrocytes do not reflect this clinical improvement. This we believe may be an indication that the dosage of AES was slightly above the optimum. Further indication of this appears in the form of slight reactions to the larger doses of AES recorded near the bottom of the tabulation.

TECHNIQUE OF DESENSITIZATION.

Accuracy of dosage is especially important in administering injections of AES for desensitization in rheumatoid arthritis because the margin between optimal dosage and overdosage is so narrow. Decimal dilutions of AES are prepared in bulk and administered from all-glass tuberculin syringes graduated in hundredths of a cubic centimeter. Neither anaphylactic nor reactions of the foreign protein type have been noted following the intravenous injection of these dilutions of AES. No local irritation appears at the sites of intradermal or subcutaneous injections. Any of these routes of administration may be used safely and with comparable end results. The size and the spacing of the doses administered in a course of treatment are all-important considerations.[3] Hard and fast rules for neither of these can be given. Much of the skill in their choice must come from experience. In an attempt to present our experience, we have selected four case records which illustrate some of the problems involved. We will refer to the more important considerations in our paragraphs of discussion after first presenting here briefly the procedure.

1. Begin treatment with the smallest recommended doses of AES (0.1 cc of dilution 10^{-18}).*

2. Repeat without increase at three to four day intervals until a clinical change and/or a change in the reading of the sedimentation of the erythrocytes is observed.

3. If these changes are favorable, the intervals between the injections of AES may gradually be increased in order to determine the length of the favorable periods. Intervals of three, five, seven, ten, fourteen, twenty-one and finally twenty-eight days have been used. As soon as a dose of AES fails to provide a favorable effect covering the desired interval, it should be increased. (See 5b.)

4. If the symptoms are aggravated by the initial dose of AES, wait for the reaction to pass, and allow a recovery period of five to seven days before giving another injection. Several repetitions of the initial amount of AES usually eliminate the reaction phase, and permits the procedure as outlined in category 3.

*It has been suggested that dilutions of this order have passed the phase of molecular dispersion, in which intermolecular forces no longer maintain molecular relationships characteristic of the original protein. This suggests the hypothesis that the biological activity of dilutes AES, upon injection, may arise from an interaction between dispersed molecules of bacterial protein and abnormal molecules of the body proteins. By this concept, allergy might be regarded as a molecular disease, and desensitization its correction at the molecular level.

5. Once a given dosage is adjusted to the individual patient's needs episodes from overdoses may be avoided by two simple precautions:

(a) An effective dose should be repeated as long as the patient is doing well, and until a slight relapse of symptoms appears during the last day or two of the intervals being used between treatments.

(b) Dosage increases should be made in accordance with the constant percentage increment schedule[2] previously published, which limits the increments to approximately 60 per cent of the dose last administered.

DISCUSSION

We have no laboratory tests by which to estimate accurately the patient's susceptibility to AES. Such a test would greatly facilitate the establishment of dosage requirements early in a course of treatment. The sedimentation of red blood cells serves as our most helpful test at present. It will frequently be of assistance in identifying overdosage of AES, when applied before and again on the third day after the early injections. A significant rise of the reading following the first dose of AES may be regarded as indicating that it has been too large. A sharp decline in the reading following the first injection of AES may be interpreted as indicating that the amount injected is near the proper amount. Such amounts, especially when followed by significant clinical improvement, may be regarded as optimal doses.

If little change in the sedimentation reading follows the first injection of AES, similar doses may be repeated at three day intervals until a trend of the sedimentation reading is determined (Table III). An upward trend should be regarded as indicating overdosage of AES.

If an optimal dose of AES is by chance chosen as the first injection in a course of treatment, clinical evidence of improvement may be noted within a few hours (Table I). This is a most striking feature of the desensitization treatment of rheumatoid arthritis. Since the optimal dose of AES varies greatly from patient to patient, the importance of a reliable objective test to determine it is evident. Much of the delay in getting a patient to respond favorably is due to delay in finding the optimal dose of AES by trial and error methods. The earliest objective evidence of clinical improvement is a decrease of swellings about the more acutely involved joints (Tables I and III). A greater range of movement accompanies this, and the subjective symptoms of pain on motion and tenderness improve accordingly. A general feeling of well being, at times amounting to euphoria, is described by the patient. This is identified objectively by a rising weight curve (Tables I and III) and by improvement in muscle tone and general strength.

The period of improvement following a single optimal dose of AES is self-limited. It may last for one or two days or for as many weeks. It is terminated by a relapse of the clinical symptoms which usually occurs as suddenly as did the erstwhile improvement. Ordinarily on the day prior to

a sharp relapse, the patient is singularly free of symptoms. Emotional disturbances are next noted. These are described variously as jitteryness; tremulousness; feeling of impending disaster; and unaccountable crying spells. A wakefulness and extreme tiredness accompanies this. The whole syndrome may last for eight to thirty-six hours and terminate in a return of all subjective and objective symptoms of the arthritis, as previously presented. By contrast these symptoms appear worse to the patient than before, but actually they are most frequently less severe than those observed before treatment.

A successful course of treatment must avoid these complete relapses. Another injection of AES at any time during the relapse phase corrects it promptly. Early in a course of treatment these relapses may be avoided by spacing the injections at three or four days (Table III), and at the same time watching the sedimentation of red blood cell readings for signs of overdosage. The intervals between injections may next be increased a day at a time until seven day intervals are attained (Tables II and III). If signs of relapse occur late in any of the periods chosen, an advance in dosage of approximately 60 per cent is made.[2] If this corrects the tendency to relapse late in the periods between injections of AES, it is repeated for as many times as it appears to suffice. The dosage is increased again if the former increase does not correct the tendency to relapse, and at any time when it appears to be insufficient to last the entire interval between injections. This tendency to relapse late in the interval between injections should be regarded as the only indication for an increase of dosage of AES.

The patient soon learns to recognize the prodromal symptoms of the relapse phases. His information may be depended upon in adjusting both the timing and the size of the doses. By gradually increasing both dosage and intervals, it becomes possible to control the symptoms with the perennial type of treatment, in which doses of AES are spaced at intervals of three or four weeks. We have encountered little difficulty in holding rheumatoid arthritis in check year after year by this perennial type of treatment.

If we allow two years for the establishment of this perennial schedule, an analysis of patients with rheumatoid arthritis now under the desensitization treatment furnishes the following:—

Number of patients under treatment with AES for more than two years—fifty-one.

Total accumulated periods of this treatment for these fifty-one patients—520 years.

Average period of treatment for each of the fifty-one patients—10.2 years.

Average period of treatment for each of the sixteen male patients—6.1 years.

Average period of treatment for each of the thirty-five female patients—12.1 years.

Patients confined to their homes, males—none.

Patients confined to their homes, females (ages fifty-three, seventy-two, and seventy-three years respectively)—3.

Overdosage of AES is indicated clinically by an aggravation of all of the peripheral symptoms of the arthritis within the first twenty-four hours after an offending injection (Table I, February 1, 1950 to June 6, 1950). Swellings about the joints increase and their movements become more restricted. Increased tenderness and soreness of the involved joints occurs regularly. General soreness of the muscles is frequently observed. Occasionally headache and anorexia are noted.

The symptoms of the milder reactions last but a few hours, and may not require the downward adjustment of subsequent doses of AES. Moderately severe reactions may last a day or two. They are usually more acute than those from gross overdosage, in which the symptoms are persistent and nagging. These reactions may last from a few days to a week or more. The patient's weight tends to decline during such periods. With the repetition of gross overdosage, the patient enters a refractory state of greater arthritic activity which appears to be little influenced by continued large doses of AES. When a patient is doing badly over a period of several weeks, it is most likely an indication of overdosage of AES. The correction of this condition may require withholding the injections for two weeks and then using a considerably reduced dose.

SUMMARY

1. A method of reversing the course of rheumatoid arthritis and of controlling it over long periods of time with a minimal amount of treatment is presented.

2. The importance of basic general management in the treatment of rheumatoid arthritis is stressed.

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EFFECTIVENESS OF A PORTABLE ELECTROSTATIC PRECIPITATOR IN ELIMINATION OF ENVIRONMENTAL ALLERGENS AND CONTROL OF ALLERGIC SYMPTOMS

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THE cleansing of particulate matter from the indoor environmental air by efficient mechanical devices constitutes one of the logical approaches to the control of environmental inhalant allergy. The principle of electrostatic precipitation of airborne particles, which has been widely utilized for the control of industrial dust and smoke problems, represents a most effective means of removing pollen and other environmental allergens from the air. Close to 100 per cent elimination of particles of 0.001 to 100 u is possible which, as may be seen from Table I, encompasses most airborne allergens, dusts, smokes, irritants, and even bacteria.[1]

TABLE I. APPROXIMATE PARTICLE SIZE (IN MICRONS, U[1])

Smallest	.2-.5 u,	smoke
(Cunningham) Zone	.1- 1 u,	fumes
2 microns	1 u,	bacteria
Medium	<5 u,	clay
(Stokes) Zone	>5 u,	sandstone
2 to 200 microns	10 u,	talc
	6-18 u,	cloud
	15-35 u,	fog
	10-100 u,	pollens
	<30 u,	spores, molds
Largest	*	fly ash
(Newton) Zone	*	saw dust
200 microns	*	cinders
	*	grindings
	*	buffings
	*	rain

*The above vary widely. Some are found as low as 10 microns, but the largest percentage is in this class.

It is well known that removal of pollen by mechanical filtration will exert some favorable influence in pollinosis, even when the efficiency of such filters in removing these particles from the air is less than 100 per cent. Improvement of pollen hay fever and asthma through the use of mechanical filtration has been reported by a number of workers.[2,6,7] Employing the principle of electrostatic precipitation, Criep and Green[3] found this method of removing dust and pollen superior to mechanical filtration, and reported excellent results when patients allergic to these substances were confined to rooms where electrostatic air purification was in operation. The large size and expense of equipment required to utilize electrostatic precipitation, as well as the cost of installation, has limited its use until recently to larger

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industrial and commercial establishments. The wider application of this principle to household dust control, and especially to allergic problems, is now fortunately receiving greater attention. Most available equipment requires installation in connection with heating or ventilating equipment,

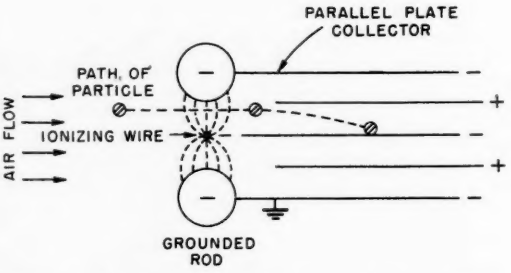

Fig. 1. Operation of electrostatic precipitator (Raytheon).

employing the duct system of the home for circulation of air through the unit. The present study reports observations on the removal of pollen, and on the control of seasonal and non-seasonal allergic respiratory symptoms, by the use of a portable, room-sized, unit of relatively inexpensive construction, requiring no installation other than connection with an ordinary electrical outlet.

PRINCIPLES OF OPERATION AND DESCRIPTION OF EQUIPMENT*

The electrostatic precipitator functions in the following manner (Fig 1): Air is drawn into the machine through a high voltage ionizer, where airborne particles receive an electrical charge. The air next passes through a cell consisting of a series of parallel collecting plates where the charged particles are attracted and adhere to plates of opposite polarity. The cleansed air is then discharged into the room. Considering that the separation of particles from the air is dependent on drift velocity of particles, spacing between collector plates, length of plates, and air velocity, the technical data supplied by the manufacturer of the equipment indicates a theoretical efficiency of 100 per cent for removing airborne particles of submicron size or larger.[8]

The precipitators utilized in this study were composed of an ionizer, collector cell, power supply, and blower, enclosed in a metal box measuring 27″x15″x15,″ and weighing approximately forty pounds. The air intake and outlet were located at opposite ends (Fig. 2). Capacity of the unit was

*The electrostatic precipitators used in this study were supplied by the Raytheon Manufacturing Company, Waltham, Mass.

rated at 200 cubic feet per minute, being capable of circulating the air of a 2000 cubic foot room, six times per hour. The power requirements were supplied by plugging into an ordinary 115 V, 60 cycle, AC outlet. Cleansing of the collecting plates was accomplished by removing the collecting cell

Fig. 2. Experimental model of electrostatic precipitator (Raytheon) used in studies.

from the machines about once a month, and dipping into a basin of hot water containing a detergent, or by spraying with a hose.

POLLEN EXPERIMENTS

The efficiency of the portable electrostatic precipitator in removing pollen from the air was determined by a series of experiments in which measured amounts of short ragweed pollen were introduced into a closed room with and without a precipitator operating. The room was thoroughly cleaned between experiments, and the pollen count ascertained to be zero before each portion was carried out.

(1) *Introduction of pollen directly into the air intake of the machine:*— The collector cell of the precipitator was first removed and three vaseline coated slides taped directly against the air outlet. With the blower operat-

TABLE II. POLLEN FALL MEASURED AFTER INTRODUCTION OF 0.1 GM. SHORT RAGWEED POLLEN INTO CLOSED ROOM, BEFORE AND AFTER PRECIPITATOR OPERATION

Conditions in Room	Position of Slide	Number of Pollen Grains per sq. cm. Slide Area at		
		0 to 5 min.	5 to 10 min.	10 to 15 min.
No air movement or precipitator operating	table	380	2	0
	chair	577	5	0
	floor	610	50	15
Precipitator operating	table	2	0	0
	chair	55	0	0
	floor	510	3	0
After 1 hour precipitator operation	table	15		
	chair	20		
	floor	71		

ing, 0.1 gm of pollen was introduced at the intake, and slides removed five minutes later for examination. These averaged 1088 grains of pollen per square centimeter of slide area.

After a thorough cleaning, the machine was allowed to operate for twenty-four hours before repeating the experiment with the collector cell replaced. Slides removed for examination after a five-minute exposure revealed no pollen deposit, indicating that the efficiency of the machine in removing particles of this size introduced directly into the air intake was 100 per cent.

(2) *Introduction of pollen into a closed room, with and without precipitator operation* (Table II):—(a) To determine the rapidity of pollen fall in a quiet room without disturbing air currents, vaseline coated slides were exposed on a table, chair, and on the floor; and 0.1 gm of pollen was distributed into the air. New slides were substituted at five-minute intervals during the next fifteen minutes. The fall of pollen was found to be greatest during the first five-minute period, becoming negligible every place except on the floor by the end of fifteen minutes.

(b) The same procedure was repeated with a precipitator operating. Exposed slides showed appreciable pollen fall at the chair and floor levels during the first five minutes, somewhat less in amount than noted without precipitator operation. During the next five minutes, however, no pollen was recovered at chair and table levels, and only a small amount on the floor. In the third period, all slides were negative. Slides exposed for an additional forty-five minutes while the unit was operating were also negative.

(c) At the completion of the above experiments the precipitator was turned off, and fresh slides exposed in the same positions. The floor was briskly swept to disturb any remaining particles, and slides were removed for reading at the end of five minutes. These showed pollen at all levels, suggesting that some pollen grains adhered to the floor and probably to

TABLE III. POLLEN FALL MEASURED AFTER INTRODUCTION OF 0.1 GM. SHORT RAGWEED POLLEN INTO A CLOSED ROOM WHERE AIR IS BEING AGITATED, BEFORE AND AFTER PRECIPITATOR OPERATION

Conditions in Room	Position of Slide	Number of Pollen Grains per sq. cm. Slide Area at		
		0 to 5 min.	5 to 10 min.	10 to 15 min.
Floor fans operating	table	104	39	24
	chair	213	35	0
	floor	270	19	4
Floor fan and precipitator operating	table	9	1	0
	chair	0	0	0
	floor	11	5	0
After 1 hour precipitator and floor fan operation	table	1		
	chair	1		
	floor	11		

other surfaces, and were not drawn into the air passing through the machine.

(3) *Introduction of pollen into a closed room in which the air is being agitated, with and without precipitator operation* (Table III):—Because of the rapid settling of pollen, the experiments in section 2 above were repeated with a strong floor fan agitating the room air.

(a) Without the precipitator operating, a more even distribution of pollen at various levels was noted, although the greatest fall still occurred during the first five minutes.

(b) With the precipitator operating, a more rapid removal of pollen from the air was evident, presumably because the air movement caused by the floor fan was successful in keeping large amounts of pollen from falling rapidly to the floor and becoming adherent to it. In this manner, more pollen was kept in the air until it could be drawn through the collector cell, where it was removed.

(c) Vigorous sweeping of the floor after one hour of precipitator and floor fan operation still resulted in recovery of some pollen, suggesting that the attraction of particles to the floor and other surfaces is not entirely overcome by the recirculation of the room air through the machine. Whether these particles, so adherent to surfaces during the operation of the unit, are of clinical importance to the allergic individual is doubtful, inasmuch as they are not in the environmental air. In the presently available commercial model of the portable electrostatic precipitator (Raytheon Micronaire), the entire machine is re-positioned, so that the air intake is at the bottom, and the air outlet at the top, instead of at the sides, as in the experimental model. This should result in increased removal of particles from the floor.

(4) *Effect of precipitator operation on pollen concentration during the pollinating season* (Table IV):—During the 1953 ragweed pollen season, slides were exposed for three successive twenty-four-hour periods in two adjacent rooms (rooms A and B), 8½x10 feet, with windows open. In

TABLE IV. COMPARISON OF POLLEN FALL IN AN AIR CLEANED AND A NON-AIR CLEANED ROOM DURING RAGWEED POLLEN SEASON

Date	Pollen Grains per sq. cm. of Slide Area Counted after 24 Hours Exposure			
	Outside Air	Location of Slide	Room A Without Precipitator	Room B With Precipitator
Aug. 26	75	table	5	0
		chair	7	0
		floor	12	2
Aug. 27	70	table	3	0
		chair	4	0
		floor	16	1
Aug. 28	98	table	8	0
		chair	7	0
		floor	10	1

one (room B), a precipitator was in constant operation, three feet from the window, and approximately midway between the window and points of slide exposure. Slide exposures were also made for similar periods on the outside window sills of both rooms. While the pollen concentration of the indoor air of room A, which had no air-cleaning unit, was only a fraction of the outside air, pollen recovery in the air-cleaned room B, was definitely less than room A.

CLINICAL STUDIES

Thirty patients were included in the study. Three were hospitalized cases, while the remainder used the machines in their own homes. These patients were each given a machine to use in one room, preferably the bedroom, for periods of one week to six months. The unit was placed on the floor of the room selected, with care that the air intake and outlet located at opposite ends of the machine were unobstructed by walls or objects. As far as possible, an effort was made to visit patients' homes to determine that the machines were properly placed, and in satisfactory operating condition. During warm weather, the windows were left open for ventilation, but strong cross currents of air through the room were avoided. Continuous operation of the precipitators was advised, even during periods when the patient was not occupying the room.

Electrostatic air cleaning was tested in twelve cases with severe pollinosis. Ten patients were allergic to ragweed pollen, and two to tree pollens. Each presented clear-cut symptoms of hay fever, asthma, or both, associated with the appearance of pollen in the air to which they were specifically sensitive. Observations were made in three patients while hospitalized, and in nine cases the precipitators were used in the home.

Eighteen patients with non-seasonal inhalant allergy were included in the study. Electrostatic machines were used during cool weather, when windows were closed and heating units in operation. Asthma was the major symptom in sixteen cases, and rhinitis the principal problem in two others. House dust was determined to be a specific allergic factor in each

TABLE V. CLINICAL RESULTS WITH ELECTROSTATIC PRECIPITATOR IN SEASONAL AND NON-SEASONAL INHALANT ALLERGY

Patient	Age	Symptoms	Sensitizations	Other Factors	Results
1	43	HF	Ragweed		+++
2	28	HF	Ragweed		+++
3	28	A	Ragweed, molds	Infection	++
4	10	HF	Ragweed		+++
5	25	HF & A	Ragweed		+++
6	27	HF	Ragweed		+++
7	42	A	Ragweed, molds	Bronchicectasis	++
8	58	HF	Ragweed		+++
9	6	HF & A	Ragweed		++
10	30	HF & A	Ragweed		HF+++ A++
11	40	HF & A	Trees		+++
12	20	HF	Trees		+++
13	8	A	Dust, foods	Emphysema	+++
14	38	PR	Dust, animal hairs		0
15	48	A	Dust, feathers, wool	Emphysema	0
16	6	A	Dust, foods	Emphysema	++
17	35	PR	Dust, physical	Infection	0
18	42	A	Dust, feathers	Emphysema, Bronchiectasis	0
19	52	A	Dust, molds, drugs	Emphysema, nasal polyps	+
20	10	A	Dust, fungi		+++
21	65	A	Dust	Emphysema, right heart failure, infection.	0
22	34	A	Dust, foods	Emphysema, infection	0
23	42	A	Dust, pollens, grass	Hypertension, right and left heart failure.	0
24	11	A	Dust, fungi, pollen	Emphysema, infection	++
25	38	A	Dust, epidermals, fungi		++
26	7	A	Dust, foods, fungi	Emphysema, infection	+
27	10	A	Dust	Infection	++
28	8	A	Dust, pollen, epidermals, foods		++
29	29	A	Dust, pollen, foods		0
30	3	A	Dust, epidermals		+++

+++—excellent improvement.
++—moderate improvement.
+—slight improvement.
0—no improvement.

HF—hay fever, seasonal.
PR—perennial rhinitis, allergic.
A —bronchial asthma.

instance, although other sensitizations and non-specific factors were present in most of these patients. It was felt, however, that indoor environmental sensitization represented a significant portion of the underlying etiology.

RESULTS (TABLE V)

(1) *Pollen sensitive cases:*—Excellent relief of symptoms occurred in nine patients, and moderate improvement in three others. Abatement of symptoms was generally noted within ten to thirty minutes after entering the air-cleaned room, lasting as long as the patient remained there with the unit operating. Prolonged relief after leaving the pollen-free atmosphere was not the rule. Symptoms generally recurred within a relatively short time after leaving the air-cleaned room, proportional to the amount of pollen present in the air and to the relative sensitivity of the patient. Three typical case histories are as follows:

Case 1. P. J., aged forty-three, had seasonal hay fever due to ragweed for fifteen years. He was seen on August 28, suffering with severe ocular and nasal symptoms, which he stated were worse at night. A precipitator was installed in his bedroom, and he reported improvement in his condition within ten minutes. He experienced complete relief each night the

machine was used. His symptoms recurred during the day while at work, but subsided very shortly after returning to his room. On the night of September 5, he was awakened by a sneezing spell, and found that the unit had stopped operating due to mechanical failure. When this was rectified, he again experienced prompt relief.

Case 4. F. V., aged ten, had severe ragweed hay fever for the past five years. He was seen on August 15 experiencing severe nasal and eye symptoms. He became progressively worse, and was given a precipitator on August 29. His mother reported almost immediate alleviation of his symptoms when the machine was placed in operation, and during the next two weeks he spent the majority of his time in the air-cleaned room. He experienced some recurrence of nasal symptoms when going into other rooms of the house for any length of time.

Case 5. P. L., aged twenty-five, experienced seasonal hay fever and asthma beginning in mid-August to frost for the past five years. When seen on August 20, he presented severe rhinitis and asthma. He was given a precipitator to use in his bedroom, and reported that the majority of his symptoms disappeared thirty minutes after starting the machine. Subsequently he slept comfortably each night, awakening with a stuffy nose. Pursuing his usual occupation during the day, away from home, his symptoms were moderately severe.

(2) *Non-seasonal cases:*—The results in dust-sensitive patients were not as clear cut as those observed in seasonal respiratory allergy due to pollen. An estimation of the degree of improvement afforded by the use of the precipitator was based on both the patient's impression and objective examination, as well as patient's requirements for symptomatic medication. As indicated in Table V, while dust sensitivity was considered to be an important factor in each patient's difficulty, other sensitizations and secondary complicating factors were generally present. The results in two cases of perennial allergic rhinitis were not striking. In three children with asthma, the results of air cleaning in the bedroom was considered excellent. Five other patients were definitely improved, but not entirely or consistently relieved during the periods they occupied the air-cleaned room. Slight improvement occurred in two cases, while six patients failed to experience any appreciable change which could be attributed to the use of the electrostatic precipitator.

DISCUSSION

The development of a simpler apparatus employing the principle of electrostatis precipitation should result in its wider application to the problems of household dust control. The excellent relief noted by pollen sufferers, and the encouraging results in cases of non-seasonal respiratory allergy,

confirming the earlier work of Criep and Green,[3] certainly warrants its continued use and further study in problems of environmental allergy.

The possibility of air-cooling or air-conditioning in conjunction with this more efficient means of air cleaning is the next logical question that arises in the minds of both the patient and physician. The influence of air-conditioning and mechanical filtration on allergic symptoms has been carefully studied by Vaughn and Cooley,[9] Gay,[4] Nelson, Rappaport, and Welker.[5] The results of these workers indicate that the favorable response observed in an air-conditioned, filtered atmosphere, appears primarily related to the cleansing of the air, rather than to cooling. Gay[4] observed that chilled air, with pollen, causes as severe symptoms as warm air saturated with pollen. Nelson and his coworkers[5] who studied patients in cooled and non-cooled filtered rooms, found a higher relative humidity in cooled rooms, and observed that symptoms in some patients were more promptly relieved in non-cooled filtered rooms, than in cooled filtered rooms. In certain asthmatic patients, the increased relative humidity appeared to aggravate rather than to alleviate symptoms. These workers concluded that such factors as increased relative humidity, rapid changes in temperature and barometric pressure, may also influence nasal and bronchial symptoms. It would appear at this time, therefore, that if air conditioning is to be considered in conjunction with electrostatic precipitation, means for the ready control of temperature and humidity are necessary.

SUMMARY

Cleansing the air of dust, smoke, pollen, and other particulate matter by electrostatic precipitation, has been in limited use for a number of years. The greater effectiveness of this method of air cleaning, as compared to mechanical filtration, is well established. In the past, the large size and expense of the equipment required to utilize this method has limited its application for the most part to industrial problems and to use in larger establishments. The possibilities of its employment for household dust control, and in the management of allergic problems, are now receiving greater attention. In the present study, observations were made with a small, portable, electrostatic precipitator (Raytheon). The ability of these units to effectively clear the air of experimentally introduced and natural occurring pollen was confirmed. During the 1953 ragweed pollinating season, electrostatic units were placed in the bedrooms and hospital rooms of selected patients suffering from ragweed hay fever and asthma. The prompt and sustained relief experienced by most patients was very striking. Electrostatic air cleaning was also found very effective in certain asthmatic patients allergic to household dusts. The results of the study indicate that this type of electrostatic precipitator will find wide application in the management of environmental inhalant allergy.

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PHARMACEUTICAL HOUSE HONORED FOR MEDICAL TV PROGRAMS

On Thursday, June 24, at San Francisco, California, Dr. Walter B. Martin, of Norfolk, Virginia, president of the American Medical Association, conferred upon Francis Boyer, president of Smith, Kline & French Laboratories, a special citation for "pioneering use of television in bettering the health of the nation." The award was made on the fourth day of the AMA annual meeting, at which color telecasts had been produced and sponsored by Smith, Kline & French. Fifty-eight programs have been presented by the pharmaceutical house at medical meetings from California to Canada and Paris, France, during the last five years.

In 1952, the "March of Medicine," a medical television program for the general public, was inaugurated to report highlights of the Chicago AMA meeting. This telecast featured a stomach operation performed at Wesley Memorial Hospital, and subsequent programs have been designed to show the contributions being made by the medical profession to the nation's health and medical progress in such fields as heart disease, cancer, obesity, and arthritis.

In conferring the citation, Dr. Martin said: "Through color television programs for doctors you have contributed immeasurably to increasing medical knowledge. Through your 'March of Medicine' programs you have portrayed to the public the vital role of the doctor—both in the research laboratory and in his treatment of the sick."

Mr. Boyer in his acceptance address stated that "this plaque is evidence of one more step in the fulfillment of an old dream—that the pharmaceutical industry would become an accepted partner of the medical profession. . . . Until a few years ago, satisfactory co-operation in medical research between a commercial house and an academic research group seemed a definite impossibility. . . . Today collaboration in medical research between pharmaceutical houses and academic research groups is the rule rather than the exception, and the award of this plaque to a commercial house by the American Medical Association is another milestone in this process of collaboration. To my mind this must be the goal of our industry. . . . Any intelligent, modern corporation knows that it must justify its existence by service, in the case of the pharmaceutical house by service to the medical profession. . . . I must say, however, that ten years ago it did not occur to me that any part of my dream of a medical-commercial partnership would be implemented through the medium of television . . . or that we would have in our building a color television laboratory staffed by ten men. . . . But there is a real reason behind Smith, Kline & French's activities in television. There is an unquenchable thirst among the medical profession for postgraduate training. There is also great need for public understanding of how the doctor of today is seeking with little thought of self to better the health of the nation."

INCIDENCE OF SENSITIVITY TO CHROMIUM, NICKEL, GOLD, SILVER AND COPPER COMPARED TO REACTIONS TO THEIR AQUEOUS SALTS INCLUDING COBALT SULFATE

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OVER THE last five years, the belief has grown that sensitivity to metals is increasing. Patients comment that jewelry sites such as the ear lobes—especially when pierced—the wrists and fingers will develop itching under or adjacent to the ornament, and the wearing of certain kinds of jewelry is apt to produce a rash. Interest in this appearance of contact dermatitis was heightened by the frequency of the ring finger being the onset location of hand eczema.[8] A group of different metals fairly representative of the composition of finger jewelry were patch tested in sixty-eight cases of hand dermatitis. Sensitivity to metal appeared in eight cases, 10 per cent in females compared to 1 per cent in males. Nickel produced the greatest number and the most severe reactions.[6]

TABLE I. TESTING MATERIALS FOR DETECTION OF METAL SENSITIVITY*

Metal Disks	*Metal Salt Solutions*
1 cm square 1 mm thick	1 per cent
Chrome (a thin sheet of steel was chrome plated)	Potassium chromate
Nickel (pure)	Nickel chloride
Gold (22 carat)	Gold sodium thiosulfate
Silver (pure)	Silver nitrate
Copper (pure)	Copper sulfate
.....	Cobalt sulfate

*The number of metals and their salts tested are increased as desired. Already, interesting data are being found from tests with amalgam and brass correlated by reactions to the salts representative of their composition.

Among the patients tested was one whose dermatitis appeared on the hands before spreading to the forearms, face, neck and feet. Severe flare-reactions were produced from patch tests with sodium chromate 0.5 per cent, and strongly positive reactions developed to dilutions of 0.2 per cent. Metal tests, including chrome plate, showed no response. If only the metal tests had been done, how easy it would have been to adjudge this patient not sensitive to chrome. This observation formed the decision to re-test a larger group of cases with metals and one of their aqueous salts. Correlations were wanted as well as proof of the specificity of any positive tests.

1. *Metals and salts tested:* The metals and their salts were obtained from an electroplating firm, a jewelry manufacturer, dental laboratory and a local pharmacist. Table I discloses the size, composition and concentration of the testing materials. The compartments of a plastic ice cube tray

were utilized to store the metal disks, and in the opposite side, the salts were kept in 15 cc dropper bottles. Solutions were made up in 100 cc lots and stored in bottles having tight plastic caps. This allowed periodic cleaning of the testing bottles, avoided contamination, and assured con-

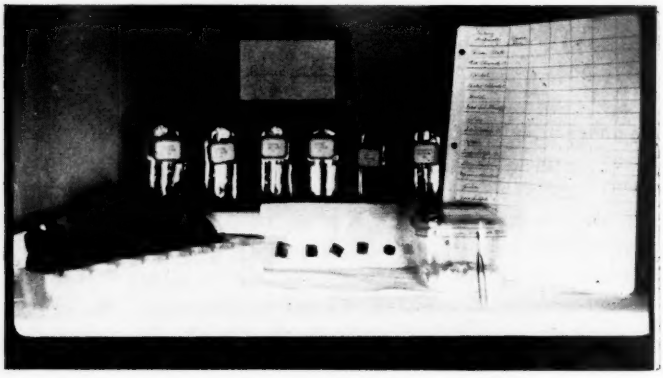

Fig. 1. Arrangement of testing materials to facilitate carrying out easily and rapidly the detection of metal sensitization. On the left is the ice cube tray for storing metal disks and testing solutions. In the background are the bottles of standard solutions and below them the strip of Elastoplast with the testing materials in place. To the right is the date sheet and container for the paper squares. The entire series of tests can be set up within two or three minutes.

stancy of the concentrations of the solutions. Filter papers were cut into 1 cm squares and stored in a plastic jar with a snug cover. Data sheets listing the metals and salts in the same order as they were arranged in the tray were also prepared.

A piece of Elastoplast, 8 by 20 cm, was used to secure the testing materials to the skin. The metal disks were arranged in a row along one side of the adhesive surface. One corner was dog-eared to stick into the adhesive to prevent loss. Opposite them were placed the filter papers. A small, pointed forceps eased their transfer. They were then moistened with the droppers in the testing bottles. Usually, the glass tip of the dropper contained sufficient solution to thoroughly wet the testing papers. As soon as the last paper was moistened, the strip was placed on the back of the patient. Setting up the entire series took about three minutes, Figure 1. The tests were read in forty-eight hours. Each patient was instructed to remove the patch if burning or itching developed. The patch was saved for several weeks in order to confirm positive tests and to identify any delayed reactions.

2. *Dermatoses tested:* The skin diseases studied appear in Table IX. This also indicates the cases in which positive tests proved of value in

determining the etiology. Negative tests were as much desired as positive ones. When 100 patients were studied the results were analyzed. The time period was the last three months of 1953, the end of a hot, humid summer in Evansville. Hydration of the skin under moisture-impervious metals, aided by moisture condensation on the metal from temperature change, seems to predispose to the development of sensitization.

3. *Criteria for accepting a positive test:** The metal disks often showed inflammatory "spot" reactions probably due to minute fissures and spurs along the borders. Occasionally these reactions would be present several days, but they were not adjudged a sign of sensitivity. They were interpreted mainly as traumatic. It was usual for the disks to induce a faint erythema. Since this faded in a day or so, it was not considered significant. This was probably an effect due to the prevention of evaporation of skin secretions. A test was considered positive if it produced itching at the site and an eruption—edema, papules and vesicles—and only if the latter persisted at least a week. Metallic nickel would sometimes produce a flare reaction. Consistently, the salts of nickel, chromate, cobalt and gold showed flare reactions, sometimes 3 to 10 cm in diameter. Symptoms and persisting signs indicated a positive test. A flare reaction indicated a high degree of sensitivity. A few pustular positive tests were observed.**

SENSITIVITY TO CHROME PLATE AND POTASSIUM CHROMATE

Wherever the eye rests today, one sees the sparkle and shine of chrome plate. Its attraction reaches into every nook of modern living. The hands, forearms, neck, thighs and legs can be in contact with it for seconds, hours or even days at a time. Furniture provides lasting contact. Children and infants may fall asleep clutching and resting on chrome plated objects. Automobiles are ideal places for continuous contact for the hands and forearms. Chrome compounds are available for painting. Anybody can purchase them. They are widely used to preserve wood, and they have an exceptionally wide range of uses on metals such as metal furniture, screens and all kinds of outdoor implements. Many people love to remove old paint so that they can repaint, and lots of people just like to paint. Home advertisers say, "Do it yourself and save," and people in all walks of life have become amateur craftsmen. Bare skin touching chrome paint or undercoatings, when the outside layer has chipped or worn off, provides an intrinsic association for acquiring sensitization.

In 1944, Hall[11] patch tested 202 aircraft employes with dime-sized metal disks coated with zinc chromate primer. One hundred and thirty-two

*The requirement that a patch test must remain positive for one week is certainly unorthodox and it is possible that important reactions to metals were not included. If metal patch test reactions persisting a day or two had been included, the total incidence of metal sensitivity would have been considerably higher.

**Pustular reactions in patch tests with metals have been described previously by Sulzberger and Goodman.

TABLE II. INCIDENCE AND COMPARATIVE SENSITIVITY TO CHROME PLATE AND POTASSIUM CHROMATE

Sex Ratio Positive Cases	Chrome Plate	Chrome Plate and Potassium Chromate	Potassium Chromate	Total Positive Tests	Total Negative Tests (controls)
Men	0	1	9	10	31
Women	0	4	2	6	53
Grand Totals	0	5	11	16	84

positive tests were obtained, and in ninety of these cases positive tests resulted from patch tests with zinc chromate powder. He noted that all workers who apply or remove this primer, or who cut, file, burr, countersink, or drill through metal coated with it, are exposed to it as an occupational hazard. Furthermore, apparently unconcerned bystanders, such as janitors sweeping up the shavings; inspectors near where the aforementioned operations are being carried out; workers repairing tools, such as drill motors and rivet guns which contain primer coated drillings, are sufficiently exposed to be sensitized. After an employe has become sensitized, even the most indirect contacts may be sufficient to initiate a flare-up of the dermatitis. In one of his patients, the dermatitis continued in severe form in spite of his absence from work until his wife, who was a riveter and not sensitive to the primer, was transferred to a job where she no longer got any primer coated drilling in her hair and on her clothing. Ellis[3] patch tested forty-seven aircraft employes with metal squares coated with zinc chromate primer. Twenty-four positive reactions were produced with four doubtful ones. These patients were then tested with sodium chromate solutions, 5 per cent, and twenty-eight positive tests were obtained. These discoveries are hard evidence that contact with chrome paint readily produces a sensitization dermatitis. One large retailer displays chrome paint, calling attention to its value as a rust preventive for metal roofs and gutters. Many rural families in this area use cistern water for drinking, cooking and also for stock if the need arises. This source of ingested chrome can be trivial or massive—pumping cistern sediment—depending upon adjustment of circumstances. Pascale et al[13] reviewed the literature on chromium intoxication, pointing out that aside from cutaneous diseases, it produces uremia, injury to the central nervous, hematopoietic and hepatic systems; and, furthermore, it can be a subtle source of systemic intoxication.

The incidence of sensitivity to chrome plate and potassium chromate is recorded in Table II. Chrome plate alone showed no positive tests. Where it did react, the salt correlated with a more severe response. An aqueous salt of chromium is a dependable test substance for detecting sensitivity. Walsh[19] thought there was good evidence for the assumption that sensitization to trivalent chromium or metallic chromium does not occur. One case has already been discussed[6] and now four more are pre-

sented. It does not appear likely that the simultaneous testing with aqueous chromate influenced the reaction to chrome plate.

Fig. 2. Location of chrome plate dermatitis. The primary source of contact was the automobile. Tests for metal sensitivity not only pointed to this source, but alerted the patient to other contacts with chrome. Positive tests proved the etiology of the hand eczema because this information brought about a resolving of the dermatitis.

Case 7.—W. L., a white man aged twenty-seven, a teacher, in the fall of 1953 carried on agriculture extension work visiting farmers. He purchased a new car and spent considerable time driving from one farm to another. Shortly after taking on this new work, the right palm began to itch and redden, and over the next few weeks small vesicles developed. The itching was more severe when driving, and the site was scratched on the horn rim of the steering wheel. About this same time, a rash appeared on the left fifth finger, Figure 2. While driving, this finger was hooked around the window lift. Treatment was ineffective; the eruption actually worsened over a two-month period. When the chrome sensitivity was discovered, improvement ensued forthwith, and in one month the hands were well. The warning for this patient was, do not touch or handle chromium.

The number of positive tests to potassium chromate seemed unbelievable. In only two cases did the history direct to chrome, Table III. This knowledge was of great value in tracing exposures and possible sources of contact with chromium and its compounds. Visits with a number of engineers brought to light the extensive use of chrome compounds in the manufacture of many different types of equipment both for the industrial and domestic market. Outdoor furniture and machinery is usually chrome processed to prevent rusting. Anodizing with chromic acid is almost a

TABLE III. SOURCE AND LOCATION OF CHROME DERMATITIS IN SIXTEEN CASES

Sex	Etiology Suspected From History	Source	Occupation	Onset Site of Dermatitis
Men				
Case				
1. J.M.	Yes	Chromic acid solution, laboratory	Chemist	Right hand, fifth web
2. G.C.	No	Diesel coolants strip mine machinery	Coal miner	Dorsa hands, generalized from overtreatment
3. A.W.	No	Anodized steel	Punch press operator	Dorsal hands
4. E.S.	No	Parts washed in chromate solution	Soldering	Dorsal hands, forearms, face, neck, back
5. R.H.	Yes	Chromate solution	Printing	Dorsal hands, forearms
6. J.R.	No	Cement	Coal miner	Dorsal hands
7. W.L.	No	Chrome horn rim, car	Teacher	Right palm, left fifth finger
8. E.G.	No	Cement?	Carpenter	Forearms, spreading to face, neck, torso, groin
9. N.G.	No	Cement	Laborer	Dorsal hands
10. L.H.	No	Paint, auto parts, coolants	Garage mechanic	Dorsal hands
Women				
Case				
1. B.H.	No	Chrome fixtures and paint	Housewife	Dorsal hands, feet, forearms and legs
2. M.B.	No	Chrome fixtures and paint	Housewife	Dorsal hands
3. S.I.	No	Paint, metal porch furniture	Housewife	Right forearm, generalizing from overtreatment
4. M.P.	No	Chrome fixtures	Housewife	Right palm
5. V.A.	No	Paint, porch furniture	Student nurse	Forearms and legs
6. O.F.	No	Sanding and painting rusted metal furniture	Housewife	Neck, antecubitals, thighs

standard procedure. The occupation of the patient was some help in defining exposure to chrome, but its use has been adopted so widely that apparently the housewife is unknowingly exposed. This is the only explanation for the discovery of chrome sensitivity in six women. All of them denied any industrial employment.

The source of the dermatitis in three cases was traced to cement. Discovering a chrome sensitivity in them was a complete surprise. Sulzberger and Baer[18] advised dermatologists and industrial physicians to "please note" the report of Jaeger and Pelloni[12] which describes potassium bichromate sensitivity in cement eczema.*

Case 8.—E. G. showed no reaction to aqueous chromate when tested on the right lower thigh, but a test at a later date on the left arm which had been involved with cement dermatitis produced such severe itching in twelve hours that the patient removed it. There followed a generalized urticarial reaction and a flareup of the previous dermatitis. When this patient was seen two days later, the test site on the left arm showed a weeping patch of dermatitis.

*Since Jaeger and Pelloni[12] reported on sensitivity to potassium dichromate in cement eczemas, numerous papers have confirmed that about 80 per cent of our cases with cement eczema have a sensitivity to potassium dichromate. The Yearbook of Dermatology and Syphilology, 1953-54 Series, by Sulzberger and Baer, contains three abstracts of European papers on chrome sensitivity and its connection with cement eczema. The author learned of these shortly before the proof of this paper was received.

Case 9.—N. G. is a white male laborer aged thirty-three. He was seen for a nummular type eczema affecting the dorsal thumbs. During August, 1951, he was unloading bagged cement from a railroad car. The second day a rash developed over the abdomen and forearms, sites of contact with the cement. The dermatitis

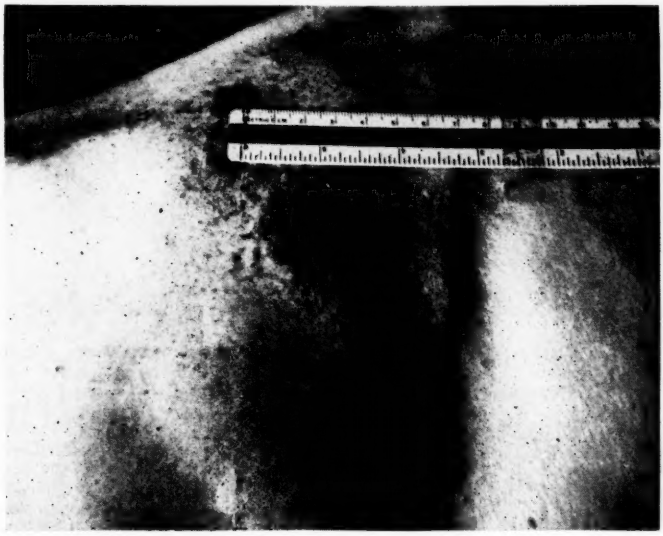

Fig. 3. Weeping patch test reaction to potassium chromate 1 per cent. This patient had a dermatitis from cement two years aggo. No explanation is offered for the linear patch of vesicles extending to the testing site of metallic nickel. This reaction is an example of the severity of the test response to potassium chromate. The patch wept for several weeks and was plainly evident eight weeks after the test. These findings helped to explain the chronicity of chrome dermatitis and the severity of the exacerbations from later exposures and contact.

soon spread with resulting partial disability for three months. Involution was complete except for the patches on the thumbs. The following summer these disappeared only to recur the next fall. A recurrence developed the fall of 1953. The patch test reaction to potassium chromate is shown in Figure 3. This case aroused speculation as to whether or not a metal sensitivity produces a cold susceptibility with the result that dry, cold weather initiates a dermatitis hiemalis.[79]

The incidence of chrome sensitivity discovered in a period of three months would appear to establish the advisability of routine testing of obscure contact eczematizations. The results were significant in hand eczema, nine out of nineteen cases in males, and three out of twenty-one in women (Table IX). Valuable clinical information was obtained from observing the severity and duration of the patch test reactions to aqueous chromate. Many of the tests persisted a month, six weeks or longer. Erythema was the last to disappear, and even when gone would brighten under

emotional stimuli. All patients were told that they should expect slow, gradual improvement over a period of four to eight weeks. The importance of an early diagnosis in metal sensitivity is shown in Figure 4.

Fig. 4. The cosmetics and especially the many topical medications appearing in this photograph were used by the wife of a physician on the basis that the remedies would relieve the symptoms and heal the existing dermatitis. The only achievement of the therapy was to worsen the dermatitis, induce spreading, and finally a generalized dermatitis developed. This necessitated hospitalization for a period of over two weeks. Patch tests showed a strong reaction to chrome metal and a flare reaction to potassium chromate 1 per cent. These reactions were interpreted as the etiologic agent in the dermatitis. The history disclosed that the dermatitis had its onset early in the summer of 1953. This patient recalled painting porch furniture about the time of its appearance. Unfortunately, the diagnosis was not made in this patient until six months later.

1. *Concentration of aqueous chromates suitable for detecting sensitization:* In 1937 Rostenberg and Sulzberger[16] tested 213 patients with sodium and potassium dichromate in dilutions of 0.5 to 1 per cent. Mention was not made of any severe reactions. Only 18 one-plus or more reactions were found, an incidence of 8 per cent. During the last fourteen years, it appears that this incidence has almost doubled. In 1939, Rostenberg and Sulzberger[15] recommended testing chromic acid as 0.5 to 1 per cent solutions, chromium chloride 2 per cent, chromium potassium sulfate 10 per cent, chromium sulfate 2 per cent, and chrome alum and chrome yellow as is. Ellis[3] had the impression that 1 per cent solution of sodium chromate made the tests unreliable and advised dilutions of 1 to 5 per cent. Winston and Walsh[20] found an 0.25 per cent solution of sodium bichromate adequate for detection of sensitivity to chromate in railroad employes working around diesel locomotives. The concentration of bichromate in the diesel radiator fluid was about 0.08 per cent. Walsh[19] tested sixty patients in a tuberculosis sanitarium with a 1 per cent solution of potassium dichromate and found three positive reactions, an incidence of 5 per cent. Sixty hospital patients tested with 0.25 per cent chromate showed no reactions. He was of the opinion that there is a higher incidence of positive tests

to 0.5 and 1 per cent dichromates in the general population than of dermatitis in industrial workers exposed to chromate. The recommended dilution for routine patch testing was 0.5 per cent, and he felt an 0.25 per cent might be a more accurate test of sensitivity. A 3-plus reaction was obtained to an 0.05 per cent solution. Engelhardt and Mayer[4] patch tested workers in photographic and lithographic trades who had had an eczema at one time or another with an 0.5 per cent solution of bichromate and found that 74 per cent of them gave positive reactions; whereas workers who had never developed a dermatitis gave 8.5 per cent positive reactions. Edmundson[2] patch tested fifty-six workers with chrome ulceration of the skin and/or nasal septum to an 0.5 per cent solution of potassium chromate. No evidence was found that these sequelae, healed or active, predisposed to chrome sensitization. Jaeger and Pelloni[12] patch tested thirty-two patients with cement eczema and 168 patients with eczema from other causes with an 0.5 per cent solution of potassium bichromate. A positive test to chromate in thirty of the cases with cement eczema allowed them to conclude that cromium salt was the actual cause. The degree of sensitivity in their cases ranged up to 0.01 per cent for solutions of chromic acid and potassium bichromate. Rostenberg and Perkins[14] found no evidence of cross-sensitization among chromium compounds—chromic nitrate, chromic chloride 2 per cent aqueous solution—in a patient sensitive to nickel and cobalt. The degree of sensitivity for cobalt was 1:10,000 and nickel only 1:200. A weak reaction to auric chloride (aqueous 2 per cent) was considered an independent sensitization.

All the patients were tested with a 1 per cent solution of potassium chromate. Eighty-four negative tests are good evidence that this concentration was not inducing primary irritation, chemical burns, or nonspecific reactions. A 1 per cent dilution was used primarily to assure detection of borderline degrees of chrome sensitivity. The principal fault with the 1 per cent concentration was the severity of the test response. Flare reactions 3, 6 or more centimeters in diameter were common. It was recommended that dilutions of 0.1 or even 0.05 per cent be routinely employed.[6]

SENSITIVITY TO NICKEL, NICKEL CHLORIDE AND COBALT SULFATE

Jewelry manufacturers have brought their wares within the reach of everyone. Infants wear rings and bracelets and keep their diapers on with pins. Teenagers, especially females, heavily decorate themselves, and quite often carry class rings around their necks by means of chains. People in the higher economic brackets appear to wear less ornamentation than those in the lower brackets. Watches have left the pockets in favor of the wrists. All these changing habits have brought about a large scale exposure of the skin to various metals. Modern metallurgy has produced jewelry that imitates the finest gold, silver and platinum. In addition,

TABLE IV. INCIDENCE AND COMPARATIVE SENSITIVITY TO NICKEL, SALTS OF NICKEL AND COBALT

Sex Ratio Pos. Tests	Nickel Metal	Nickel Chloride	Nickel Metal & Chloride	Cobalt Sulfate	Nickel Metal & Chloride, Cobalt Sulfate	Total Pos. Tests	Total Neg. Tests
Men	0	0	1	0	0	1	40
Women	0	0	6	0	6	12	47
Grand Total			7		6	13	87

TABLE V. LOCATION AND SOURCE OF NICKEL AND NICKEL COBALT DERMATITIS

Sex	Etiology Suspected From History	Source of Sensitization	Occupation	Onset Site of Dermatitis
Men				
Case				
1. R.D.	Yes	Wrist watch	Barber (scissors and clippers had to be taped to prevent dermatitis)	Hands, spreading to face and neck from overtreatment
Women				
Case				
1. A.F.	No	Nickel plated grids	Assembled radio tubes	Right flexor surface of 1, 2, 3 fingers
2. M.B.	No	Necklace	Beautician	Left neck
3. R.J.	Yes	Wrist watch	Housewife	Left wrist
4. E.D.	Yes	Glasses	Nurse	Ears
5. E.S.	Yes	Wrist watch	Housewife	Left wrist
6. M.C.	No	Glasses	Housewife	Ears
7. A.K.	No	Not Known	Secretary	Face
8. E.W.	Yes	Wrist watch	Housewife	Left wrist, generalized dermatitis from overtreatment
9. C.B.	No	Wrist watch battery case	Housewife	Left wrist, generalized dermatitis from overtreatment
10. C.B.	No	Wrist watch	Clerk	Dorsal hands, 2 previous attacks of generalized dermatitis from rash on left wrist
11. P.P.	Yes	Garter	Housewife	Left thigh
12. M.B.	Yes	Wrist watch furniture	Nurse	Left wrist, left thigh

metal fasteners, hooks, eyes, pins, buckles, clips and zippers are excellent exposure contacts, as well as furniture and vehicles.

The incidence of sensitivity to nickel and cobalt appears in Table IV. This is distinct and separate from that of chrome. The sex ratio is impressive. Equally significant is a comparison of the sensitizing properties of nickel compared to chrome. Nickel always reacted with its salt, but never showed as intense reaction. Half the cases showed a concurrent sensitivity to cobalt. Rostenberg and Perkins[14] surveyed numerous sources of encountering cobalt. Its use as a pigment in enamels and paints provides exposure similar to chrome. All positive tests to cobalt were associated with reactions to nickel and its salt.

The etiology of dermatitis from jewelry was suspected with greater frequency than that from chrome, seven out of thirteen cases. These patients were aware that jewelry would produce itching and a rash, but they showed no inclination not to wear it, often shifted it to another area

of skin with the same events produced. Even this led them to ignore it and declare the problem to be "bad nerves." Four patients had to experience a generalized dermatitis from overtreatment, three of whom were hospitalized, before they realized the sensitizing potential of nickel.

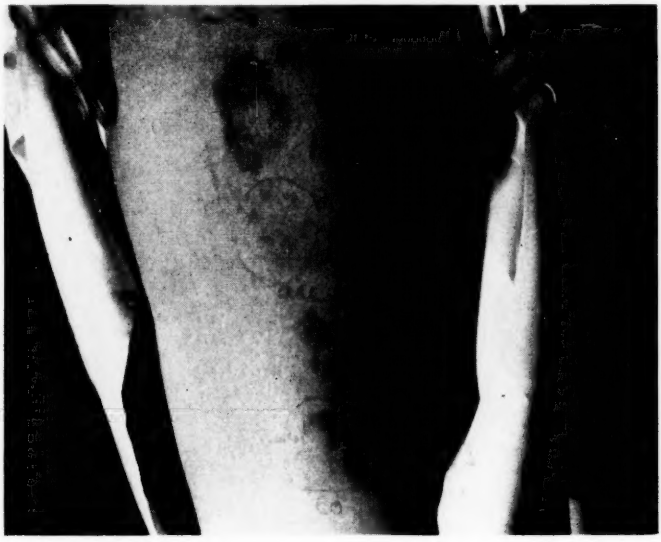

Fig. 5A. M. B. was seen early in December for a patch of dermatitis affecting the left wrist and left thigh. She could not believe that a prized possession like a wrist watch would produce any irritation. At this time, she refused patch tests, but in January decided to have these done. This accounts for the January date appearing on the patch test reactions. The flare reaction to nickel chloride is plainly evident, also the positive reaction to nickel metal. A reaction to gold is just appearing and a similar intense reaction to silver metal. A flare reaction to cobalt is plainly evident. The tests were done on January 11, and the photograph was taken five days later.

In five cases the demonstration of metal sensitivity allowed the detection of the etiologic ornament. Each patient was told over and over again that any itching of their skin or rash pointed to contact with metal until proven otherwise, Table V.

M. B., a white woman aged twenty-four, was seen for a chronic patch of dermatitis affecting the left wrist and left thigh. This was of two years' duration The patch test reactions are shown in Figure 5, A and B.

1. *Concentration of nickel chloride and cobalt sulfate for detection of sensitization:* In 1937, Rostenberg and Sulzberger[16] tested 228 subjects with nickel sulfate 5 per cent. They found twenty-eight reactions of 1-plus

or more. In 1939, they recommended 5 per cent concentrations of nickel nitrate and 5 to 10 per cent for nickel sulfate.[15] Cormia and Stewart[1] employed nickel chloride and cobalt chloride in concentrations of 8 to 10 per cent. Two of their cases reacted with positive tests at previous sites

Fig. 5B. This shows the reaction to the gold salt seventeen days later. The patch of dermatitis on the left wrist is also shown. The gold reaction persisted with more intense symptoms than any other metal and its salt. These reactions are good examples of the chronicity of dermatitis from metals. It was not felt that any of the reactions represented cross-sensitization, being instead multiple sensitivities from contact with different metals.

of dermatitis, but negatively when normal skin was tested. Rostenberg and Perkins[14] used 2 per cent nickel nitrate and cobalt nitrate for detecting sensitization. Goldman[10] tested his patients with 1 per cent and 10 per cent concentrations. Foster and Ball[5] used a 5 per cent concentration. Sulzberger[17] stated that 2 to 5 per cent solutions of nickel sulfate caused no reaction in normal skins, and this concentration will not cause positive eczematous response unless there is a real eczematous sensitivity to nickel.

All patients in this study were tested with a 1 per cent aqueous nickel chloride. Eighty-seven negative tests is good evidence that this concentration was not inducing primary irritation, chemical burns and non-specific reactions. The principal concern of this concentration was the intensity of positive tests. Flaring was the rule, 3 to 9 centimeters were common, and in some cases as much as 15 centimeters. Higher dilutions were not tested, but it would seem that a concentration of 0.1 per cent would be adequate for detecting sensitization.

TABLE VI. INCIDENCE AND COMPARATIVE SENSITIVITY TO GOLD AND ITS SALT

Sex Ratio	Gold Metal	Gold Metal & Gold Sod. Thiosulfate	Total Pos. Tests	Total Neg. Tests
Men	0	0	0	41
Women	0	1	1	58

TABLE VII. INCIDENCE AND COMPARATIVE SENSITIVITY TO SILVER AND ITS SALT

Sex Ratio	Silver Metal	Silver Metal and Silver Nitrate	Silver Nitrate	Total Pos. Tests	Total Neg. Tests
Men	0	1	0	1	40
Women	0	0	0	0	59

SENSITIVITY TO GOLD AND GOLD SODIUM THIOSULFATE

The jewelry manufacturer who prepared some of the metal disks commented about the substitution of materials that have affected the industry. The noble metals, gold and silver, have apparently been replaced more and more by alloys. Some of the alloys are such good imitations that no gold or silver is used as base metal. The trivial incidence of reactions to gold and its salt, Table VI, is good evidence that substitution in ornamental manufacture accounts for the increasing number of patients with metal sensitivity.

L. B., a woman aged twenty-three, was being treated for acne vulgaris. The history revealed several attacks of hand eczema always beginning on the left ring finger and associated with the wearing of a gold ring. She agreed to wear the ring again to see if it would produce a recurrence. After three weeks and during a spell of warm weather, a typical recurrence developed under and adjacent to the ring over the dorsal surface of the ring finger. A persistent erythema was obtained from gold, 22 carat, and gold sodium thiosulfate produced a papular dermatitis.

SENSITIVITY TO SILVER AND SILVER NITRATE

What has been said about gold holds true for silver. Only one case was found (Table VII). Some reactions to silver nitrate might have been missed because the darkening of the test site might have obscured any response. An advantage in using silver nitrate is that it permitted ready placement of the test patch on the skin because of the stain on the skin as well as on the patch.

R. B., a white man aged fifty-five, presented a dry, fissuring, scaling dermatitis affecting primarily the tips of the fingers. The left palm showed a similar involvement. The dermatitis appeared ten months ago, shortly after he became a postmaster. All day long he handled coins. The manner in which he picked up

TABLE VIII. INCIDENCE AND COMPARATIVE SENSITIVITY TO COPPER AND ITS SALT

Sex Ratio	Copper Metal	Copper Sulfate	Copper Metal and Copper Sulfate	Total Pos. Tests	Total Neg. Tests
Men	0	0	0	0	41
Women	0	1	0	1	58

coins, counted them, and removed them from the old fashioned wood till corresponded exactly to the site of his dermatitis. Pure silver produced a bright erythema which in a few days became a dry, scaly patch. A dime was also tested, and this produced pustules, probably due to presence of alloys. The reaction to silver nitrate was distinctly vesicular. When inspected one week later, it had become a patch of scaly dermatitis, 2 cm in diameter.

SENSITIVITY TO COPPER AND COPPER SULFATE

This metal behaved similarly to gold and silver, Table VIII. A greenish staining of the skin was a common accompaniment to contact with copper metal. A trivial follicular reaction was common.

M. W., a white woman, aged twenty, presented an acute vesicular dermatitis affecting the left palm and adjacent two, three, four and five fingers. The copper sulfate reaction brought to mind a recent habit of sleeping with a sacred emblem tightly clutched in the left hand. The dermatitis healed promptly when this practice was stopped.

CLINICAL VALUE OF PATCH TEST WITH METALS AND THEIR SALTS

The Evansville area is the center of refrigeration and air conditioning manufacture. There is, in addition, a body and assembly plant of a large automobile corporation. Strip mining, too, is a major industry as well as oil production and refining. Scattered throughout the city area are dozens of small plants turning out tool and metal part accessories. The range of industrial activity brings the hands into contact with many diversified materials. Most of the people live in single unit homes, maintaining their yards, gardens and household repairs. An office worker may paint the basement walls one week-end, and the next cover the floor with asphalt tile. Business and professional people are apt to remodel the attic, paint the fence or tinker for hours with their power lawn and garden machinery. Housewives are forever decorating here and there, painting things or changing one item for something else. All these human activities are going on day in and day out, and permit manifold exposures and contacts with the constant stream of new products, vying for positions of eminence in the market.

The final results of patch tests with metals and their salts are shown in Table IX. They cannot be interpreted as static. They are merely an indication of what people were doing in the summer and early fall of 1953.

TABLE IX. CLINICAL VALUE OF TESTING FOR METAL SENSITIVITY IN VARIOUS DERMATOSES

Skin Diseases	Men	Metals			Women	Metals			
		Cr	Ni	Ag		Cr	Ni Co	Au	Cu
Hand eczema	19	9	1	1	21	3	2	1	1
Pedal dermatitis	3				1				
Seborrheic dermatitis	1				2				
Ear eczema	1				5		2		
Occipital eczema	0				2				
Alopecia areata	0				1				
Ano-genital dermatitis	3				3				
Psoriasis	0				2				
Vitiligo	0				1				
Dermatitis venenata	8	1			13	3	8		
Atopic dermatitis	1				0				
Acne	1				0				
Folliculitis	1				0				
Dermititis hiemalis	0				2				
Lupus erythematosus	1				1				
Dermatitis legs	0				6				
Dermatitis medicamentosa	1				0				

A positive patch test is not construed as solving the etiology in any given case of hand eczema. It is considered an important finding; and if the knowledge it furnishes helps to resolve a dermatitis, then and then only is the testing information worthwhile. Even in the presence of such an obvious set of facts as a dermatitis on the wrist demarcated by the clasp and bracelet of a wrist watch, not too much is gained in certain patients by telling them to stop wearing the watch. However, when they feel on their back or thigh, the itching of a positive nickel patch test and see a big red spot, this is something different. Now they are convinced. One patient had to try her earrings two different times before she was convinced, and another had to induce a dermatitis on both breasts before she believed the battery case from her hearing aid was at fault.

SUMMARY

Patch tests with metals and their salts is a simple, quick procedure for detecting apparent or hidden metal sensitivity. Thirty-two cases were found in a period of three months. Hand eczema and dermatitis venenata comprised the majority of cases. In Evansville, metal sensitivity, especially in males, is an important part of the etiologic background in hand eczema. No evidence was found for cross-sensitization between metals and their salts. In one case, the pH of the testing solution was thought to influence the reaction, but that phase of the problem was not investigated, nor has the salt content of the sweat been studied in relation to reactions.

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SCHERING CREATES FOUR NEW RESEARCH DIVISIONS

Schering Corporation announced early in June the creation of four new divisions in its expanding laboratory research program. In 1953, this pharmaceutical manufacturing firm spent 9 per cent of its total receipts from sales on research, and the new organization plan is designed to further this emphasis on the study of new compounds and new production methods.

A Division of Biological and Therapeutic Research, under the direction of Dr. Edward C. Reifenstein, Jr., will carry on bacteriologic research, investigate living tissues, and study initial administration of new drugs in human beings.

Dr. S. W. Lee will administer the Division of Medicinal and Pharmaceutical Research and will co-ordinate the efforts of the chemical and biological groups.

A Division of Chemical Research and Development, headed by Dr. E. B. Hershberg, will handle the field of bio-synthesis.

Dr. Bradley Whitman will direct the new Research Services Division which is responsible for budgeting and service functions of the research and development activities of all Schering's investigative work.

Dr. Domenick Papa has been named Assistant to the Vice President and charged with the responsibility for patent administration and scientific contacts throughout the world, in an effort to investigate and co-ordinate research outside Schering's own laboratories.

In announcing the new research program, Francis C. Brown, president, stated: "Schering intends not only to supply new drugs to the medical profession, but also to support each new product with precise studies concerning therapeutic boundaries and mechanisms of action in human beings. . . . The medical profession can be assured that our products will have the widest experimental data behind them, and that they will have maximum safety and efficacy in treating the conditions for which they are intended."

A TENTATIVE QUALITATIVE AND QUANTITATIVE CLASSIFICATION OF THE ASTHMAS

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AS INTERNISTS practicing allergy, our conversations and communications frequently concern asthmatic patients. The classical descriptive terms as, for instance, extrinsic or intrinsic, are so general, or else the classifications as "allergic," "infectious" and "cardiac" have, in most cases, been so incompletely defined, that it is difficult for us to tell each other, or, for that matter, to record for posterity exactly what we mean.

We owe so great a debt to our predecessors that we must, in the very beginning, note that the historic terms did serve an important, and useful, purpose. When the far reaches of allergy were vague, these broad outlining terms helped delineate some of its boundaries. In the light of our present knowledge, however, the types of asthma we meet undoubtedly require re-classification. As a matter of fact, the asthmas, as such, have been re-classified in actual practice. This has, however, not so far been done in print, excepting recently by Dr. Oscar Swineford, whose thinking in many ways independently runs parallel with ours. Dr. Halpin and I hope that our present paper will tend to crystallize today's knowledge, and so will serve, temporarily, at least, to stabilize our descriptive vocabulary, perhaps until new facts concerning asthma are discovered, resulting, in due time, in the publication of superseding classifications.

At first we attempted to break down the types of asthma into a classification based on etiology, anatomy, physiological and functional derangement. This gave us a classification with Arabic and Roman numerals using, in all, thirty terms, and obviously much too complex and cumbersome for daily use. We were more successful when we limited ourselves to defining in broad outlines the types of asthma, and re-defining the degrees of severity. Given these, generally, any author describing an asthmatic patient could easily add specific terms as concerned with anatomical and physiological changes.

Since we all are, as practicing allergists, competely familiar with the historical definitions, they will neither be listed nor defined.

We begin by taking wheezing as our predominant sign and symptom, and find that there are at least eight clearly defined syndromes, although they can, and do, overlap. Their features are, nevertheless, so distinctive that they can, with ease, be differentially diagnosed.

TYPES OF WHEEZING

1. Atopic.
2. Infectious (a) acute, (b) chronic.
3. Psychogenic.
4. Physical.
5. Nasogenic (or reflex).
6. Cardiac.
7. Locally obstructive.
8. Asthma due to drug reactions.

Let us define them in turn with the understanding that they represent only skeleton outlines and that qualifying terms must be used.

ATOPIC ASTHMA

Personal History: Other previous or present atopic disorders are frequent.

Family History: Often positive for atopic disease.

Onset of Wheezing: Abrupt and Intermittent.

Clinical Course: Predictable (exposure, environment, or season.)

Physical Examination: Mucous membranes pale, translucent, Sinuses clear, or membranes symmetrically thickened. Lungs: Sounds change in pitch and intensity from area to area. Few, if any, other complaints.

Pathological Findings: Completely reversible (excepting in longstanding untreated patients.)

Laboratory data: Mucoid secretions, with eosinophilia. Blood: normal. Frequent eosinophilia. Right Weltmann.

Skin Tests: Multiple positive reactions.

Response to Treatment: Excellent with Epinephrine, Ephedrine, Aminophylline and Steroids, with complete elimination, and for specific injection therapy with causative inhalants.

INFECTIOUS ASTHMA (ACUTE)

Personal History: Previous atopy, rare.

Family History: Atopic disorders, rare.

Onset of Wheezing: Usually gradual, or may be abrupt.

Clinical Course: Not predictable, excepting as occurring with successive infections.

Physical Examination: Mucous membranes red, opaque. Sinuses opaque, often unilaterally affected. Broncho-spasm, with mucous rales and signs of infection. Few other disorders.

Pathological Findings: Reversible in early stages.

Laboratory data: Secretions: purulent. Blood: W.B.C. usually elevated. Basal sedimentation rate elevated after several days of illness. Right Weltmann. Skin Tests: negative, or non-specifically positive.

Response to Treatment: Poor, or transient, for Epinephrine, Ephedrine and Aminophylline. For injection treatment with vaccines; variable. With chemotherapy; good, if combined with steroids, excellent.

INFECTIOUS ASTHMA,(CHRONIC) WHEN NOT SUPERIMPOSED

ON OTHER DISORDERS

Personal History: Negative, or rare, for atopy.

Family History: Negative, or rare, for atopy.

Onset of Wheezing: Gradual, with history of chronic infection, increasing dyspnea on exposure to pulmonary irritants, gaseous, chemical, or particulate.

Clinical Course: Exacerbations successively increasing in severity and duration.

Physical Examination: Majority of patients have normal mucous membranes which are sometimes red and injected. Sinuses: free of disease, or chronically infected. Lungs: emphysematous, with diminished cardiac dullness, diminished breath sounds, low diaphragms, prolonged expiration. Prominent accessory respiratory musculature.

Laboratory data: Secretions mucoid or purulent. Blood: normal, with increased sedimentation rate. Left Weltman. Skin tests: negative.

Response to Treatment: Good with antibiotic agents. Poor to medications, depending upon amount of infection and destruction. The response depends upon the presence of bronchitis, emphysema, bronchiectasis, pneumonoconiosis. The patient is often relieved by physical measures, postural drainage, belts, and prone position.

This clinical picture may be more typical of our patients in Boston and Cedar Rapids than it may be of those, say, in Orlando and Houston.

PSYCHOGENIC ASTHMA

Personal History: May be positive for atopy, but present attack not related to exposure, environment or season.

Family History: May be positive for atopy (imitative asthma).

Onset of Wheezing: Abrupt, during or following emotional stress.

Clinical Course: Depends upon continuation of stress, strain, or neurotic purpose of attack. Multiple complaints.

Physical Examination: Rapid or sighing respiration, with subjective distress not proportional to objective signs. High vital capacity, with false results checked by pulmonary function studies. Evidence of hyperventilation. Patient can be diverted to talk or eat, especially in hysterical types of response.

Laboratory Data: Normal, excepting for gaseous exchange data.

Response to Treatment: Excellent with sedation and placebos. Good with psychoptherapy or intravenous Ambobarbital. Occasional dramatic response to anticholinergic agents.

PHYSICAL ALLERGY, WITH WHEEZING

May occur alone rarely or in conjunction with other types. Clean-cut history of bronchospasm following exposure to sudden heat, cold, as affecting the skin, inspired air, or the gastrointestinal tract.

NASOGENIC ASTHMA (REFLEX)

May occur alone or in conjunction with other types. History of effects of cold air and fumes as affecting the nostrils, and reflexly to polyps, and pathological lesions external to the rest of the upper respiratory tract.

CARDIAC ASTHMA

Personal History: Negative or positive for allergy.

Family History: Negative or positive for allergy.

Onset of Wheezing: Late in life, gradual, in prone position.

Clinical Course: Depends on treatment of cardiac disorder.

Physical Examination: (?) Cyanosis. Tachycardia, Arrhythmias, accentuated pulmonary second sound; prolonged circulation time, and pulmonary congestion during (but not between) attacks. (?) Hypertension. Occasionally no obvious signs of cardiac disease or congestive failure.

Laboratory data: Depends on cardiac lesion.

Response to Treatment: Slow, but good, for hyponatric diet, Digitalis, diuretics. Orthopneic position for sleep. Immediate response to morphine and to Aminophylline, excellent.

LOCAL OBSTRUCTIVE WHEEZING

Personal History: None for atopy or infection.

Family History: None for atopy or infection.

Onset of Wheezing: Usually abrupt, if following aspiration of foreign body (?) Aneurysm, if present, gradual onset.

Clinical Course: Rapidly increasing debility if the foreign body is not removed.

Physical Examination: Localized stridor. Unequal respiratory excursion, although wheezing may be bilateral. (?) Visible collateral circulation (veins.) (?) Enlargement of glands or spleen. (?) Cyanosis or orthopnea. Evidence of carcinoma (? 20 per cent), Thyroid nodules, Hodgkin's Disease. Sarcoid, Multiple Myeloma, Tuberculosis glands and Bronchiolitis deformans.

Pathological Findings: Depend on type or position of foreign body.

Laboratory Data: Depend on type and position of foreign body.

Response to Treatment: Depends on what, where, and how long.

ASTHMA DUE TO DRUG AND CHEMICAL REACTIONS, NOXIOUS VAPORS AND FUMES

Personal History: May be negative in Aspirin sensitivity, positive in Penicillin sensitivity. May be positive for infectious asthma or nasogenic asthma.

Family History: Usually negative for allergic disorders.

Onset of Wheezing: Abrupt or may take several hours.

Clinical Course: May respond to medication, but may last for weeks, months, or years.

Physical Examination: Variable, from mild wheezing to status asthmaticus limited to lung alone or accompanied by nasal, oral, gastrointestinal tract, gland and skin manifestations of reaction.

Pathological Findings: Usually completely reversible.

Laboratory Data: Depends on the drug and the method of challenge. Tests may be positive or negative.

Response to Treatment: Good, but temporary for Epinephrine, Ephedrine, and Aminophylline. Excellent for ACTH and Cortisone.

Of course, all these syndromes can conceivably overlap. An atopic patient can get infected, inspire a foreign body, be emotionally upset, develop cardiac lesions. We can, however, use our classification as follows:

Asthma, atopic
- with acute infection
- with chronic infection
- with psychogenic factors
- with physical allergy
- with nasogenic features
- with cardiac disorders
- with local obstructive lesions
- with drug reactions.

With acute infectious asthma (omitting the atopic and chronic elements), we can say.

Asthma, infectious, acute,
- with psychogenic features
- with physical features
- with nasogenic features
- with cardiac disorders
- with local obstruction
- with drug reactions.

With chronic infection, there can be psychogenic, nasogenic, cardiac, or locally obstructive lesions, or drug reactions. On the other hand, as we go down the list, types of wheezing above and below become less likely. As, for instance, drug reactions are less likely to have local obstruction, just as local obstructive lesions are likely to occur in cardiac disease.

Cardiac asthma is unlikely to be affected nasogenically. Certainly physical factors, as cold air and effort, may exacerbate cardiac disorder, but more likely in the direction of angina of effort than in true cardiac decompensation. Psychogenic effects may bother any patient, typically as seen in the wheezing due to hyperventilation.

Having defined our types, we must agree on severity, as based on pre-asthmatic and post-asthmatic findings, combined with the responses to treatment, remembering that etiological factors can be progressively cumulative.

The traditional numbers 1, 2 and 3 can be used for mild, moderate and severe asthma, with "status asthmaticus" keeping its present label. If we check the literature and case reports, we discover that the term "mild", or Grade 1, refers to the following qualities:

Mild response to major exposure, in quantity or time.

Quick recovery following elimination of exposure.

Quick response to remedial substances of mild effect, as potassium iodide, or small doses of strong remedial agents, as epinephrine.

Freedom of symptoms until next exposure.

All these undoubtedly, because of their functional nature, occur only during attacks. We can almost postulate with certainty that the absence of signs or symptoms, or lowered vital capacity between attacks, represents early, or mild, asthma.

Grade 2, or moderate asthma, responds more vigorously to less exposure, and requires more time and stronger medication for relief. Such patients, when sensitive to pollen, begin early in the season, respond less completely to air-conditioning, take larger doses of Ephedrine and Epinephrine, and may require small doses of ACTH and Cortisone. Their symptoms may extend beyond the season because their lungs are triggered, because other causes exist, or because there is no complete restoration to normal between bouts of asthma.

Our grade 3 severe asthmatic patient responds more vigorously to allergens, and stays sick longer. The more heroic measures are less completely effective. This group is more exactly defined as one having a lowered vital capacity in total amount, or by pulmonary function studies, of 40 per cent or more below normal.

At some point, in all types of asthma, our severely ill patient may present degenerative, fibroblastic and obliterative changes, and little or no response to environmental or climatic change. Of course, any patient can go into Status Asthmaticus with overwhelming exposure, or with multiplicity or cumulatively active bronchospastic agents. Status Asthmaticus is, therefore, best regarded as separate from the others, not only in degree, but in type.

Have we any right to these definitions of "mild," "moderate," and

"severe"? An examination of 4,000 histories shows that objectively there are, at first, only functional changes, with reversibility and freedom between attacks, progressing to pulmonary function depression between attacks, often, at first, only obvious to the patient as easy dyspnea with effort, emotion, or laughter. In severely asthmatic patients, there is measurably lowered vital capacity, with the patient responding less and less to more and more treatment. The changes are now obvious also to the physician. The patient in Status Asthmaticus is obvious to everybody.

Granted that we have a workable classification, where may it fall short? The first criticism of such systems is that they may be awkward to use. So is any classification until the user becomes familiar with it. When the Standard Nomenclature was first introduced, there was a general clamor that it not only caused additional work but served no useful purpose. Time has proven this, in some cases, to be due to inertia rather than to a fault inherent in the codification system.

The second criticism of such classifications is that they do not include every present or conceivable possible future asthmatic state. Human beings and diseases, being what they are, do not permit exact classification. We have to do the best we can with what we have, and modify our classifications as time and experience prove it desirable to have them otherwise.

The third criticism is usually a statement to the effect that we ought to say what we mean. Why use any classification at all? If every internist who is practicing Allergy would define, in every case report, the chief etiological factor, the contributing or causative factors, the degree of patient response, the predominant tissue effects, and the progressive pathological changes which occur, no classification would be necessary. But anyone who will so define his patients will find that he has translated our classification into general medical language. He will find it just as easy to analyze his patients in terms of the classification, using modifying data.

The cardiologists have long since found it useful to label their patients in accordance with numbers, and in terms of Etiology, Anatomy, Physiological and Functional disturbances. Smithwick and his associates have coded hypertension into four grades, according to a weighted set of values. If we want to use thirty or more terms, we can do this for asthma, but I doubt the time is ripe for so cumbersome a terminology.

Whether we use the classification presented here, or some other set of better terms, does not matter. What is important is that we do something we are not doing now—and that is, define our asthmatic patient's state so that each of us knows what the other means. If any other method of achieving this aim satisfactorily, exists, it might be well at this time to pool the best talents available, so that work on this problem of paramount present importance can be completed to everybody's satisfaction.

DISCUSSION

LAWRENCE J. HALPIN (Cedar Rapids, Iowa): A satisfactory, workable code or classification of the asthmas must be brief, clear and easy to use. It must be as all-inclusive as possible but not to the point of being a chore to decipher, apply or interpret. The American Medical Association's "Standard Nomenclature of Diseases and Operations" is used by 91 per cent of federal hospitals and 74 per cent of all hospitals in the United States.[1] The latest edition of this volume lists asthma with no descriptive subheadings or classifications other than psychogenic. Doctor Brown's summation of our thoughts presents a classification that is easily applied, thus permitting clarity and understanding between physicians.

A year ago one of us was describing an asthmatic patient in terms to imply that the severity was of marked degree. There was no agreement among us as to the proper basis for estimating severity. We found that severity-description differed in individuals as well as in geographical location. What was severe to one man was considered as moderate to another with the east, south, mid-west and west using as many variable classifications as there were physicians.

What is gained by stating that the patient has "asthma"? Compare this with a descriptive diagnosis using our code: "asthma, ragweed, with acute infection, class 2" or "asthma, infectious, chronic, with emphysema, class 3." In this latter example, adequate clinical expression would read somewhat as follows: "The patient has asthma due to chronic infectious bronchitis. Emphysema is present. He responds less vigorously to medication now than he has in the past. His symptoms are more prolonged, and his vital capacity shows 40 per cent or more below normal. He requires more medication and more heroic measures to provide any measure of relief." To emphasize Doctor Brown's statement, in each example we have defined the chief etiological factor, the contributing factors, the degree of patient response, the predominant tissue effects and the progressive pathological changes which have occurred. With this comparison, we feel that a standardized classification of asthma, as presented, is indicated for, and usable by, all physicians. The coding can be expanded, simplified or modified to meet any needs.

The use of such a classification should be valued by physicians, hospitals, life insurance companies, selective service boards—its application is far-reaching. The only requirement is proper orientation of those who employ this means of expression.

Certainly there is little enough standardization in this specialty of allergy. We feel that standard terminology and classification is an important basis for clear understanding among ourselves and between allergy and other specialties.

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ANAPHYLACTIC SHOCK AND DEATH DUE TO PENICILLIN
Report of a Case

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Houston, Texas

THE FOLLOWING case is not unique or unusual but, because of the immediate severity of the reaction and the fact that we were able to perform an autopsy, we decided to follow the suggestion of Collins-Williams and Vincent[1] and make it a matter of record.

K. W., a thirty-eight-year-old white man, who had been apparently in good health, developed a slight cold and sore throat and was given 300,000 units of Duracillin® about 6:45 A.M. by his wife, who was not a nurse nor a medical technician. She had given her husband penicillin on three or four previous occasions for upper respiratory infections without any mishap. Immediately following the injection, however, generalized urticaria with intense itching, shortness of breath and constricting pains in the chest developed. The family physician, who lived across the street, was called to see him. The patient was immediately given 0.5 cc of epinephrine hydrochloride, 1:1000, subcutaneously, and 2 cc of Benadryl®, subcutaneously. As there was generalized inspiratory and expiratory wheezing of the mucous type and as the patient ceased to breathe and no heart sounds were heard within three minutes after administration of the epinephrine, 1 cc of epinephrine hydrochloride, 1:1000, was administered directly into the heart. At the same time, artificial respiration was begun and continued for twenty minutes, at which time a resuscitator with oxygen arrived with the Emergency Corps and this was used for thirty minutes. The patient expired approximately fifteen to twenty minutes after the time of the injection of the Duracillin.®

The patient had had one previous episode of urticaria which caused discomfort and constricting pains in the chest. It subsided within an hour after 50 milligrams of Benadryl® was given by mouth. This had occurred approximately six weeks earlier. The cause of his previous urticaria has never been determined and no evidence of penicillin administration could be obtained. It is suggested by the patient's wife that this episode had been caused by a sensitivity to an aromatic liniment used for sore muscles one or two hours before the onset of urticaria. No history of asthma or other allergies could be obtained.

An autopsy on this patient was performed approximately two hours post mortem.

NECROPSY FINDINGS

External Examination: A well-developed, well-nourished white man, 73 inches tall and 205 pounds in weight. There was no evidence of trauma. There were two small pinpoint penetrating wounds noted, one in the precardium and the other in the gluteal area in the left upper medial quadrant.

An incision was made in the gluteal area following the site of this injection and although it was blood tinged, no gross blood was present. No area of trauma was noted in the deep tissues nor were any of the visible vessels punctured.

The primary incision was that of a "T" following the area of both clavicles and a midline incision coming to the left of the umbilicus down to the area of the symphysis pubis. The peritoneal cavity was dry, the intestines were not distended and there was evidence of trauma or burns in the gastric mucosa. The pericardial cavity contained approximately 5 cc of a serous fluid. The pleural cavity contained

only a trace of serous fluid. The right lung was free of adhesions. There were, however, moderate and dense adhesions over the entire lateral and posterior area of the left lung. There was an area of atelectasis about 5 cm in diameter near the apex of the left lung. No abnormalities were noted in the mediastinum.

Lungs: Weight—right, 400 grams. Left—600 grams. In the main bronchus (upon being cut) was approximately 30 cc of thick tenacious mucus which was readily removed.

Aorta: A minimal amount of atheromatous plaques were present. The remainder of the post-mortem findings were negative. The microscopic studies of the tissues in this case were non-contributory.

SUMMARY

A check with the Lilly Laboratories, through our local representative, relative to the lot of penicillin used on this patient revealed that no other unusual side effects had been reported to them.

We have reported a case of an immediate anaphylactic reaction due to penicillin resulting in death where reaction was so rapid that the usual eosinophilic response expected in the lung tissues and its secretions were not seen in the microscopic examination. There have been a few cases of anaphylactic reaction following procaine penicillin injections reported in the medical literature but this is much more common, as can be determined by personal communication with other physicians.

There is the possibility that this fatality might have been due to an intravenous injection of procaine penicillin since it is an insoluable salt and will produce death when given intravenously, but no evidence of intravenous injection was discovered at autopsy.

REFERENCES

1. Collins-Williams, C., and Vincent, J.: Sensitivity reactions to penicillin in children. Ann. Allergy, 11:454-469, 1953.

808 Caroline (Dr. Etter)

ALLERGY TO MONOSODIUM GLUTAMATE

Dr. Leo H. Pollock of Kansas City, Missouri, reports in the June 19 issue of *The Journal of the American Medical Association* an instance of allergy to monosodium glutamate in a mother and her son. The offending agents could not be found for some time, and other children in the family were not affected.

The allergic symptoms were manifested by epigastric fulness, eructations, distention, and upper abdominal discomfort, but x-rays of the gall bladder and upper intestine were normal. These patients would become sick within half an hour after eating, whether at home, at parties, or in restaurants. Nicely prepared foods, such as roasts, steaks, spaghetti with mild sauces, caused distress, but no other persons present at such meals showed any symptoms.

Monosodium glutamate was finally recognized as the offending agent, and the symptoms disappeared when the patients avoided all foods in whose preparation it had been used. This product is an ingredient in many canned soups, canned beef gravy, seasoned salt, and certain canned vegetable juices.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

AUTO-ANTIBODIES VERSUS SPERMATOZOA

Antigenicity of body-own substances has often been investigated, and the possible role of auto-antibodies in disease has widely been discussed. However, the technical difficulties in obtaining evidence are great. In two fields only has important progress been made. The first is that of the antigens of the Wassermann and Forssman group. The second concerns the corpuscular constituents of the blood. Here the results have indeed been spectacular.

A remarkable report on an auto-antibody is found in the current issue of the *Proceedings of the Society for Experimental Biology and Medicine* (Vol. 86: p. 652). It occurs in a system other than the blood. In two male subjects, an agglutinating antibody against spermatozoa was discovered in significant titers, present both in the serum and in the seminal plasma. All human spermatozoa tested, including those of the subjects, were clumped. Both subjects were sterile, but no impairment of the spermatozoa excepting these antibodies could be detected. Whether the immune reaction provides a clue for the explanation of the sterility remains to be seen. But above and beyond this question, the general biological interest of these observations is obviously great.

Interestingly enough, the work was done by a busy physician (Leo Wilson) who had no more technical apparatus than a microscope, a centrifuge, and an incubator. In these days of large research organizations and complex instrumentation, it is good to see that important contributions to medical science can still be made with simple techniques if the investigator retains the ability to observe and the willingness to take pains.—*A.J.W.*

ARALEN® AND ATABRINE® CLEAR LIGHT-SENSITIVE ERUPTIONS

The Journal of Investigative Dermatology (22:11, 1954) reports a study made at Keesler Air Force Base at Biloxi, Mississippi, by Drs. John M. Knox, John H. Lamb, Bedford Shermire, and Robert J. Morgan, in which various light-sensitive eruptions, some of twenty years' duration, were completely cleared, or the patients showed dramatic improvement, after treatment with the antimalarial drugs Aralen or Atabrine (Winthrop-Stearns).

Aralen is the drug of choice in light-sensitive dermatitis and lupus erythematosus. The authors report 90 per cent clearing of severe plaque-like eruptions within five months with Atabrine in a patient who had been on continuous hormone therapy, plus application of a light-screening ointment, for nineteen months with only 30 per cent improvement. "Response to Aralen or Atabrine was quicker and successful in a higher percentage of cases," they said, and no side reactions were noted in this study.

Progress in Allergy

BRONCHIAL ASTHMA

A Review of the Recent Literature—1953

PHILIP M. GOTTLIEB, M.D., F.A.C.A.
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Since the last review of the advances in bronchial asthma,[114] the medical literature has continued to accord the subject great attention. In the period from November, 1952, through January, 1954, the Current List of Medical Literature indexed 411 articles under the title of asthma, comprising about 0.33 per cent of the total listings. About 62 per cent of them were in languages other than English. Percentage-wise, these figures compare closely to those of the previous year.

The articles consulted ran the gamut from a case report and discussion by a senior medical student,[24] through a presentation of what the general practitioner should know about asthma,[151] to detailed and erudite investigations of the pathophysiology of respiratory dysfunction. The new text by F. K. Hansel[128] contains several excellent chapters on asthma.

Continuing interest in objective methods of evaluating ventilatory function in asthma, the use of the oximeter in assessing causative factors and therapeutic efforts, and the employment of cortisone and corticotropin in treatment may be singled out as dominating the current trends in investigation. In addition, a large number of studies are concerned with assaying the effectiveness of various therapeutic agents and approaches.

The arrangement of the material, aside from minor changes, and the general orientation previously followed[114] will again guide the present review.

INCIDENCE AND MORTALITY

Employing a screening technique in a survey sponsored by the Richmond Department of Health and the Richmond Academy of Medicine in collaboration with the United States Public Health Service, Blanton and his coworkers[31] determined the incidence of respiratory allergic diseases and certain non-allergic conditions in 37,497 persons. Asthma was present in 975 individuals or 2.6 per cent; in comparison, seasonal hay fever was found in 1,135 subjects or 3.0 per cent, and "perennial hay fever" in 161 cases. Extension of the percentage figures leads to an estimate of 3.5 million cases of bronchial asthma in the United States. Allergic conditions occurred twice as frequently in the white population as in the colored. No marked differences were found in respect to sex or age. As a group, the asthmatic subjects tended to weigh more and to be better educated than the total population screened. They were also more likely to have concomitant hypertension, diabetes mellitus or pulmonary tuberculosis, but somewhat less likely to have anemia or heart disease.

Johnston[148] cited the findings of Louis O. Dublin of the Metropolitan Life Insurance Company that bronchial asthma along with hay fever is the third most common chronic disease in the United States, and that about 5,000 persons in this country die annually from bronchial asthma.

Williams[292] has extended his statistical studies on asthma in England and Wales (the previous article was abstracted in last year's review[114]) to determine the incidence of death from status asthmaticus. In England about one person in each 110 was found to have asthma; in the years from 1930 to 1949, asthma accounted for 7.07 deaths per 100,000 population. This is considerably higher than the figures for the United States, given as 1.6 or 1.7 deaths per 100,000 population. He found the death rate to be slightly higher in male than in female asthmatics. To indicate the frequency of deaths from asthma, he describes eleven fatalities in the single year of 1951 among a few hundred patients in one clinic, and he has records of forty-one deaths in status asthmaticus. About 90 per cent of his asthmatic fatalities were over thirty years of age, although two-thirds of the cases treated were below that age. Other sources are in substantial agreement, since in 140 fatal cases culled from the literature (largely of American origin), 82 per cent were over thirty years of age, as were 96 per cent of the Registrar-General's 3,106 recorded asthmatic fatalities for the year 1949. Most fatal cases have had asthma for a considerable period of time. In Williams' series, 81 per cent had had the disease for more than five, 66 per cent for more than ten, and 54 per cent for more than twenty years. However, the American experience differs somewhat, the figures being 53, 33 and 18 per cent, respectively. Moreover, there seems to be a smaller group of asthmatics with the disease starting in middle age and soon developing into severe status asthmaticus from which death ensues in a few years. The conclusions seem warranted that asthma carries a definite mortality rate from status asthmaticus, that death occurs predominantly in middle-aged and elderly asthmatics, and usually in those with chronic asthma and those prone to develop status asthmaticus.

Williams found that a breakdown of the annual fatality rate showed low monthly levels for the summer months, a sharp rise in November, and peaks in January, February and March, dropping through April to low levels in May. The curve showed a remarkable parallelism to the death rate from bronchitis. The findings are attributed to the dominant part played by infection in the causation of death from status asthmaticus. It would be of interest to know if the findings would be similar for the United States.

Despite the detailed statistical studies of Williams; Bullen; and Rackemann and Edwards, all reviewed last year,[114] the *Lancet* comments editorially,[80] "The prognosis of asthma, like that of many other recurrent conditions, is still largely a mystery. . . . This study should prompt us to discard the complacent belief that palliative treatment usually suffices. The asthmatic child or adult should be carefully investigated *at the onset* of symptoms and a rational régime instituted forthwith." No one who has observed the clinical course of a number of asthmatics would be likely to quarrel with this viewpoint, yet only too often is such advice disregarded.

A statistical review of 400 cases of asthma in veterans of World War II observed by Fein[91] at San Antonio, Texas, between July, 1945, and July, 1951, revealed some points of interest. About 54 per cent of them had a past history of allergic disease prior to entering military service and 81 per cent of them had received medical discharges because of asthma. In 76 per cent the asthma was considered service-connected or service-aggravated. A follow-up six years after separation from military service

showed that 28 per cent were asymptomatic, 44 per cent mildly, 23 per cent moderately and 5 per cent severely asthmatic.

In a three-year period, the Permanente Foundation Hospital admitted 200 patients with bronchial asthma, thirty of them twice, fifteen three times, and eighteen four or more times, including one with seven admissions, according to Dannenberg.[67] Below the age of fourteen years, males outnumbered females by a ratio of 2:1, while the ratio was reversed for those between fifteen and forty-five years of age; beyond the age of forty-five years the sex distribution was approximately equal. The average hospital stay was 4.36 days. Only two deaths occurred. In a breakdown by months, most admissions occurred between May and July, corresponding to the major pollen season in the San Francisco Bay area, with somewhat lower figures between December and February. The fewest admissions were in March, April, August, September and October, corresponding to the minor pollination period and the least inclement weather. The curve of incidence by months would certainly be different for other areas of the country.

CLINICAL PATHOLOGY

Water balance was studied by Pipkorn[200] in forty-eight cases of asthma by means of the Volhard test. Urine specimens were collected every half hour after the patient drank 1,000 ml of tea. Thirteen cases had a urinary output of less than 430 ml (ten of them had asthma for more than five years) and twelve other cases, an output between 430 and 650 ml. The intravenous administration of 200 mg of Antistine® increased the urinary output 10 to 50 per cent under these circumstances in eight-ninths of the cases in which it was tried, and this increase was greatest in the patients with the longer histories of asthma. After intramuscular injections of thyroxin, the urine output was decreased in sixteen of twenty-nine subjects, but Antistine tended to correct this. The mechanism of fluid retention in some cases of asthma and the mode of action of Antistine in regulating this is unknown.

According to Bachmann and Ruiz Moreno,[12] the detailed and systematic examination of the bronchial secretions in asthma has not received the attention it merits; it is particularly helpful in assessing to what degree bronchial infection contributes to the symptomatology in cases of chronic asthma with multiple sensitivities. The sputum is studied for the number of bronchial cells, neutrophils, eosinophils, lymphocytes, plasmocytes, monocytes, histiocytes, macrophages and erythrocytes, and the amount of mucus and nuclear débris. In a number of cases of asthma and acute and chronic bronchitis, the sputum examination correlated with clinical and roentgenographic findings. It assisted in classifying the asthma as "pure allergic," "complicated allergic" or "nonclassified asthma with bronchial infection." Demonstrable bronchial infection was found in 63 per cent of the specimens from asthmatics, and the cytologic examination of the sputum was a useful guide in both diagnosis and treatment.

Andersson[7] noted that one-half hour after the hypodermic injection of 0.5 mg of histamine, the blood eosinophils were decreased in normal subjects, but increased in asthmatics. More frequent determinations on one asthmatic patient showed the highest eosinophil count after ten minutes, but still above the base line after sixty minutes. Andersson suggests that if these findings are valid, the eosinophil response to histamine may be a diagnostic aid.

Although his studies involved parasitized African natives in Tanganyika rather than asthmatic patients, Vaughan[286] showed that there is a considerable, though not absolute, association between eosinophilia of the blood and of sputum. He suggests that eosinophilia of the sputum and the preceding eosinophilic infiltration of the lungs are integral parts of a general eosinophilia in such cases.

Eosinopenia similar to that produced by the injection of corticotropin or cortisone can also result from emotional stress, such as occurs prior to a medical school examination or before an operation, according to Dreyfuss and Feldman.[76] The reduction in circulating eosinophils averaged 42 and 44 per cent. These observations help to explain the variability of normal eosinophil counts, and emotionally induced eosinopenia may interfere with the interpretation of counts performed during steroid therapy.

ETIOLOGY

Numerous investigations and case reports attest the multiplicity of causative factors involved in the clinical syndrome of asthma. Some widely-held viewpoints have been re-evaluated, and in the opinion of some, found wanting. The significance of heredity in asthma (see below) and the concept of asthma as a disease of adaptation have been questioned. Turiaf[276] in France has concluded that there is no clear evidence of adrenal cortical hypofunction in asthmatic patients. Asthma is not associated with Addison's disease. Eosinophilia is a dubious criterion of hypocorticism since it is not demonstrable in a considerable number of cases. When present, it is more markedly reduced by ACTH than by cortisone; the opposite relation would obtain if there were a state of cortical insufficiency. These hormones owe their effect in asthma to their pharmacologic action, rather than to any influence on, or replacement therapy for, a hypofunctioning adrenal cortex. Selye's concept of the general adaptation syndrome is based on endocrinologic experiments on animals and has never been convincingly demonstrated in human disease, and more especially, not in human asthma.

A scholarly dissertation on the immunologic aspects of asthma and other allergic diseases has been contributed by Spain.[260] In immunologic terms, asthma may be subdivided into (1) the skin-sensitive or wheal type (immediate reaction type), mediated by skin-sensitizing (histamine-releasing) antibodies or blocking (not histamine-releasing) antibodies; and (2) the skin-negative or nonwheal type (delayed-reaction type), which may be subdivided into (a) the noninfective or (b) infective forms, the nature of the antibodies not being known in either form. The mechanism of aspirin sensitivity, usually occurring in patients with the infective type of asthma, is unknown. The evidence for bacterial asthma, often with a hereditary feature like other types but of unknown immunologic mechanism, consists in part of the large local reactions sometimes produced by autogenous vaccines, and the occurrence of stubborn asthma or even status asthmaticus after small doses of vaccine.

Sutherland[268] found the allergic factor to be demonstrable in about 70 per cent of his cases of asthma, but the causes were obscure in the remaining 30 per cent. Included as possible factors in this group were infections, particularly in the paranasal sinuses, reflexes, dyspepsia, endocrine disorders, and emotional upsets. The common association of aspirin-sensitivity

and nasal polyps is noteworthy, but the situation is confused by the fact that aspirin is not infrequently of therapeutic benefit in asthma.

In a study of the apparent causes of 2,000 cases of asthma, A. Brown[40] found chilling to be mentioned as an important etiologic factor with surprising frequency. In this large series, asthma first occurred after bronchitis in 817 cases; after chilling in 472; after hay fever in 158; for no apparent cause in 153; after pneumonia in 132; in association with eczema in 89; after ether anesthesia in 65; after whooping cough in 50; after measles or scarlet fever in 32; after war gassing in 21; in association with byssinosis in five; after inhalation of chlorinated water in three; after inhalation of sea water in two; and after convulsions in one case.

Heredity.—On the basis of his animal experiments,[220,221] of the family histories of asthmatic patients,[225] of a critical analysis of the literature, and of an evaluation of the monograph of Schwartz (reviewed last year[114]) on the subject, Ratner and Silberman[224,225] found themselves unable to accept the hereditary concept of allergy. In about 40 per cent of the family histories of 250 patients, comprising an average of twenty-five persons per family, there was only one allergic member, the patient himself; in an additional 25 per cent, only one other relative exhibited allergy. Less than 1 per cent of the families had striking allergic pedigrees of the type so often cited, indicating the extremely low incidence of such an occurrence. Re-evaluation of the protocols of the publications of Cooke and others revealed similar data. Ratner also found, in contrast to several published studies, that there was no correlation between the type of family history and the age of onset of allergic symptoms in his patients. In the total population of these families, comprising 6,244 individuals including the patients, 9.8 per cent were allergic, a figure entirely comparable to that for the general population. While agreeing with many of Schwartz's conclusions, Ratner raises several questions concerning his classification of allergic diseases and his selection of control material. It is concluded that the available data does not satisfactorily demonstrate that, within the scope of the antigen-antibody mechanism, the capacity to become sensitized is controlled by genetic influences. However, no claims are made of any proof that the gene does not play a role in the production of the allergic state. It is extremely difficult to dissociate acquired from genetic factors in its establishment. The conflicting conclusions of attempts to apply Mendelian laws to allergy indicate that no genetic hypothesis can be made to fit the existing data.

An editorial comment[82] on this stand grants that published data fall short of conclusive proof of the heredity of allergy. Part of the difficulty lies in deciding which disease states are truly allergic, and in confusion regarding doubtful or "minor" allergies. However, the implications of clinical observations are strongly suggestive, even though it cannot be determined whether the hereditary factor is a Mendelian dominant, a recessive or intermediate. Actual observation of the children of parents who have themselves been completely studied may prove far more instructive than retrospective family histories.

Bowen[37] has approached the problem in interesting fashion in studying fifty-nine pairs of identical (monozygotic) twins. A careful check of the obstetrical records confirmed each pair to have been monoplacental. Contrary to earlier observations, coexisting allergy in both twins was the exception rather than the rule, occurring in only seven sets. In the

remaining fifty-two pairs only one member had asthma (some with concomitant nasal symptoms). These findings cast doubt on the hereditary concept of asthma and on the concept of placental transference of allergic manifestations. The early onset of symptoms in many of the children and their occurrence in only one of each pair seem to refute the maternal rejection theory of the psychodynamics of asthma. The possibility that maternal dietary restrictions during pregnancy will reduce the incidence of allergy in the newborn is likewise challenged.

Inhalant and Occupational Asthma.—The recent republication[199] of an article from the December 27, 1843, issue of the *Boston Medical and Surgical Journal* clearly shows that inhalants were fully acknowledged as causes of asthma over one hundred years ago. Dr. Patterson himself suffered severe paroxysms on the inhalation of small amounts of ipecac powder or on merely entering a room where ipecac had recently been spilled, even though it was cleared away and the room aired. Ingestion of ipecac also caused symptoms. Interestingly, he recognized the fact that infinitesimal quantities were sufficient and that his asthma followed many years of allergic rhinitis, which he terms "catarrhal affection."

E. A. Brown and Colombo[44] have again directed attention to fumes, odors and smells as causes of asthma. A detailed questionnaire, which is reproduced in full in this article, was found to be helpful in disclosing such cases. In fifty successive private cases of asthma, seven responded affirmatively. A casual search of his files impresses this reviewer with the possibility that the true incidence may be much higher. The relationship of the asthma to the fumes or odors in these instances is clear cut and specific. It does not appear to be a reflex response, since not all sharp or acrid smells cause difficulty, but only one type or one group of odors affects any one patient. The response is often instantaneous, and may vary from slight annoyance to major bronchospasm. Skin tests are negative. Such cases, if incompletely studied, may be misconstrued as "intrinsically asthmatic" and will, for obvious reasons, improve in a different geographic location. While it is sometimes difficult to be certain that there is no inhalation of particulate matter, in many instances dilutions of essential oils or osmyls so attenuated as to be barely noticeable may cause alarming symptoms.

The list of such asthmogenic fumes and odors is long. Important examples include plant and flower odors, tobacco smoke (although other mechanisms must be considered), flour, paint and linseed oil, range oil, kerosene, turpentine, solvents, cleaning fluids, bleaching fluids, wood and coal smoke, perfumes, moth balls, waxes and insecticides.

A recent query[212] concerning a shipping clerk in a paint and varnish factory raises the question of nonspecific irritation from the vapors of paint and varnish as against the specific allergenic effect of linseed and other products.

Workers in grain elevators and feed mills are exposed to high densities of dust from crude grains and frequently acquire a disabling respiratory disease of asthma-like character. The dusts are complex mixtures containing the bristles and other particles from the outer coats of grain kernels, spores of smuts and rusts, insect débris, pollens, field dust, and other organic and inorganic materials. Presumably, grain dust is intrinsically more irritating to the respiratory mucosa than refined flour dust. Cohen and Osgood[56] studied eleven instances of grain handler's disease, characterized by progressive dyspnea, cough and frequent wheezing. Eight cases

were incapacitated. The length of exposure before symptoms appeared varied from ten to thirty-five years. Wheezing or sibilant and sonorous expiratory and inspiratory râles were present in all cases on one or more occasions. The roentgenograms of the chest were not characteristic but several showed emphysema and/or increased lung markings. The vital capacity was usually reduced. Six cases were classified as atopic on the basis of history and skin tests, to a variety of allergens; five of them were skin-sensitive to crude grain dust and four of them also to refined flours. Two of the nonatopic patients had positive skin tests with crude grain dust extract, but these reactions were considered irritative. In two cases the skin tests were inconclusive. Four patients died, and three necropsies are reported in full. They showed emphysema and marked interstitial, peribronchiolar and peribronchial fibrosis without bronchiectasis; two had evidence of cor pulmonale. It is concluded that grain handler's disease may result from prolonged exposure to crude grain dust in allergically sensitive workers, but that this is not the only causative factor in its production. Incapacitating respiratory symptoms and pulmonary changes can ensue in the absence of allergic sensitivity.

Small[256] issued a warning concerning the increasing importance of castor bean as an allergen—there are thousands of acres in California devoted to its cultivation in addition to 20,000,000 pounds imported annually. It is being widely used in ground form as pomace for fertilizer. This involves large-scale handling by agricultural, railroad, trucking and warehouse employes. Furthermore, the contamination of trucks, box cars, and warehouses with castor bean dust is difficult to remove, so that other commodities subsequently transported or stored in these facilities will also carry some of the allergen.

Two interesting reports of occupational asthma come from England. Fowler[99] reported thirty-two cases in printers due to inhalation of a spray of gum-acacia dissolved in isopropyl alcohol. The workers are exposed to an intense mist in color-printing processes. Twenty-six of the cases had no past or family history of allergy. An additional fourteen printers presented symptoms of early and milder sensitization to the spray fluid. The average length of occupational exposure before the asthma appeared was 4.8 years, but was only half as long for those with a past or family history of allergy. The time of exposure necessary to produce paroxysms varied, but the majority occurred between one and seven hours. Relief was noted within one to six hours after leaving work. The severity of the attacks appeared to vary with the amount of the spray inhaled.

Frankland[101] found four cases of asthma among thirty-four laboratory workers in experimental research stations in England in close contact with two kinds of locusts, *Locusta migratoria* and *Schistocerca gregaria*. Some technicians also developed allergic rhinitis and skin irritations. Fourteen other workers gave positive skin tests, one of them subsequently developing asthma. There has been no previous account in the English language of locusts causing allergic symptoms, although a Spanish report appeared in 1935. Locust feces seemed more allergenic than the whole locust body. Hyposensitization with an extract of locust feces was successful in one case. Although difficult to quantify, it appeared that the degree (and duration) of exposure affected both the degree of sensitivity and the time taken for subclinical symptoms to become manifest. There seems to be cross-antigenicity between locusts and cockroaches, which are entomologically allied. Studies among persons in contact with swarms of locusts in the field should prove of interest.

In response to a query,[213] it has again been pointed out that the exact incidence of asthma as a sequel of hay fever is not known, but it may be estimated that about 40 per cent of patients with hay fever sooner or later develop bronchial asthma unless they receive injections of the specific extracts of the offending pollens. Such treatment, if given adequately and in time, will almost certainly prevent the onset of asthma in at least 95 per cent of cases.

A simple skin test with cottonseed in a case reported by Juhlin-Dannfelt, Schnabel and Wiholm[150] produced a tremendous local and a very severe constitutional reaction. Daily skin test titres and provocative (inhalation) tests performed daily for the next twenty-two days showed no subsequent significant reduction in cutaneous or bronchial hypersensitiveness, reactions being elicited with high dilutions of cottonseed antigen. The administration of ACTH resulted in no great change in this regard. There was no evidence of a refractory period in the hypersensitiveness after the allergic shock.

Cobb[55] pointed out that if pillows, mattresses, cushions, upholstered furniture, automobile upholstery, stuffed toys, and the like were manufactured only with foam rubber or other suitable nonallergenic synthetic material, there would result a great reduction in the incidence of asthma, as well as of vasomotor rhinitis and to some extent allergic eczemas. The cost factor would be controlled by the enormous increase in the use of the substitute materials. If this suggestion could be followed, one might anticipate a considerable reduction in the incidence of sensitivity to such common antigens as cottonseed, feathers, kapok and animal hairs.

A disease known locally as "Yokohama asthma" has been a health problem in the American military forces since 1946. The condition is seasonal, prevailing from September or October through March or April. The symptoms, usually occurring in the late evening or early morning, range from a mild bronchial irritation to severe respiratory distress requiring emergency therapy. A previous history of asthma is uncommon. While it may occur elsewhere in Japan, as a health problem it is endemic to Yokohama, and patients are relieved on moving short distances away. A two-year study by Redfearn and Karakawa[227] of the 406th Medical General Laboratory revealed no relationship to air-borne pollens, few of which are present between November and February, or spores. The incidence of "Yokohama asthma" was found to correlate with air pollution and certain weather factors. The closest correlation, although still incomplete, involved aire-borne dust and ether-soluble aerosols, the latter including organic acids, ketones, unsaturated hydrocarbons, peroxide organic compounds and other substances. From the meteorologic viewpoint, wind velocity, rainfall and particularly temperature inversions seemed to be implicated, but apparently only as determinants of smog. The problem is said to be comparable to the smog of industrial cities such as Donora, Pennsylvania, or Los Angeles, California. The authors concluded that further study of this complicated relationship of case incidence, weather and air pollution is needed. One may add that is also necessary in many localities other than Yokohama..

Molds and Fungi.—In addition to the generally accepted role of air-borne fungous spores as inhalant allergens, fungi are claimed to produce asthma by other mechanisms—when infecting the bronchopulmonary tissues according to van der Werff[284] or as a result of absorption of allergens from dermatomycoses according to Hajós and his coworkers.[124]

van der Werff[284] believes that among the possible causes of intrinsic asthma, bronchomycoses and pneumonomycoses deserve attention. It would appear that the continued presence of pathogenic fungi in the respiratory tract may itself become an internal source of allergens, causing asthma in previously non-asthmatic individuals. The clinical course of mycotic infections of the lung is variable and may include bronchitis, bronchopneumonia, indurative pneumonia or chronic pneumonitis, with or without the formation of cavities; it may simulate pulmonary tuberculosis. The presence of large numbers of nonpathogenic fungi and yeasts in the respiratory tract leads to difficulty in evaluating sputum cultures, and animal inoculations may be necessary to prove pathogenicity: serologic or allergic reactions are sometimes helpful in this respect. Two pertinent cases are reported with bronchitis and pneumonic infiltrations, becoming fibrotic and in one case, cavitational, due to a new *Trichosporon* species and to *Aspergillus amstelodami* (Mangin), respectively. One patient apparently acquired the infection while harvesting rye, the other while working in a cucumber hot house employing a fermented horse manure fertilizer. Both showed marked skin reactions to extracts of the causative fungi, and a close parallelism between the number of fungus colonies and the asthmatic and bronchitic phenomena before and after therapy. Antibiotics and sulfonamides appeared to be ineffective, but short courses of neosalvarsan led to cessation of the asthma and disappearance of the fungi. Neufeld and Wallbank[194] observed a case of *Candida* asthma with a sputum rich in colonies of *Candida albicans*. Aerosol therapy of a 10 per cent solution of sodium caprylate in propylene glycol for four weeks rendered the sputum free of *Candida* and the patient free of asthma. Coincidental tuberculous lesions were not influenced.

Hajós, Petö and Pogány[124] performed 4,589 intradermal skin tests with eighteen different mold and fungus allergens on 446 cases of bronchial asthma. A high incidence of delayed reactions occurred, as follows: *Achorion schönleini* 13.8 per cent; *Alternaria* 4.75 per cent; *Aspergillus* 13.3 per cent; *Epidermophyton* 8.1 per cent; *Mucor* 7.7 per cent; *Penicillium* 14.2 per cent; and miscellaneous *Trichophyton* species 17.7 per cent. Mycotic skin disease was present in 15 per cent of these asthmatic patients. The cause of sensitization to *Achorion* was not clear. The deeper cutaneous mycoses seem more likely to sensitize. Prausnitz-Küstner passive transfer was successful in twenty-eight of forty-four trials with *Trichophyton, Epidermophyton, Mucor, Aspergillus,* and *Penicillium*. Inhalation tests were negative with the first two agents, but were positive with the others. It is postulated that in dermatomycoses the allergens enter the blood stream, are transformed into endo-allergens and reach the shock tissue in the lung hematogenously. The mechanism is comparable to the causation of mycids and dermatophytids. In patients with both dermatomycoses and asthma a symptom-free period of over one year could be obtained by a six to eight week course of hyposensitization.

Air-borne fungus studies were performed in Brunswick, Georgia, by Collier and Ferguson[57] and in New Brunswick, New Jersey, by Schaffer, Seidmon and Bruskin.[240] Both groups employed cultural methods. In the Georgia study, the dominant molds of the twenty-eight identified were *Penicillium, Alternaria, Oospora, Aspergillus* and *Monilia*. Seasonal variations showed peaks for *Penicillium* in the fall, and for *Alternaria* in the first months of the year, although both were present throughout the year. *Aspergillus* was found in the greatest numbers in September, with low

counts in the other months. *Oospora* and *Monilia* each occurred almost exclusively in the spring. Wind variations had a marked influence on the counts and rainfall seemed to cleanse the atmosphere.

The New Jersey study[240] recovered fifty identifiable and culturable fungi, the most common of which were:

Hormodendrum	*Pullularia*	*Botrytis*
Penicillium	*Aspergillus*	*Fusarium*
Alternaria	*Cylindrocarpon*	*Helminthosporium*
Epicoccum	*Stemphyllium*	*Phoma*

These presented a perennial curve, low in the winter months, rising in March, reaching a peak in July, and falling to February. The remaining thirty-nine genera, including one not identified, were not as numerous nor as important clinically, with a few exceptions; they showed a plateau-like curve of yearly incidence with the lowest point in May. Temporary conditions of climate or plant pathology favoring any one fungus may produce variations in these curves. House dust cultures yielded thirty-six of the fifty fungi found in the air; the twelve most frequent included nine of those listed above, and also *Mucor, Rhizopus,* and *Scopulariopsis.* Air slides and centrifuge studies were used to recover non-culturable fungus spores such as smuts, rusts, mushroom, mildews and puffballs.

Intradermal skin tests in patients with seasonal or nonseasonal asthma and/or vasomotor rhinitis gave three plus or four plus reactions in variable proportions of patients: 30.4 per cent with *Alternaria,* and in smaller percentages with other fungi. Treatment of 106 patients over a two-year period with one to ten fungus extracts gave excellent results in 38.7 per cent, good in 42.5 per cent, and fair in 13.2 per cent. It is concluded that there is a definite correlation between the colony counts of air-borne fungi and positive skin test results, and that with a few exceptions, the most constant fungi are the most significant clinically. Viable fungi are present throughout the year in large numbers in house dust and play an important role in causing perennial symptoms in certain patients. Non-culturable fungi, smuts, rusts, mildews, and mushroom spores are also of clinical importance in the area studied.

According to Gregory and others[117] tremendous numbers of spores of dry rot (*Merulius lacrymans*) were recovered from the air in a condemned bomb-damaged house in London, reaching levels of 360,000 spores per cubic meter in the cellar. However, in an undamaged old cottage no spores of dry rot were present and less than ten spores per cubic meter of any kind.

Foods and Nutrition.—Gutmann[119] observed the effects of partial starvation on allergic disease in Jerusalem during the spring and summer of 1948, when virtual siege conditions led to extreme shortages of food, particularly animal protein, fruits, vegetables and salad greens. The average daily adults intake fell to 670 calories. There was a noticeable improvement in chronic asthmatic patients, many of whom became practically symptom-free. It was shown that this was not attributable to food allergy *per se.* At the same time, the response to epinephrine was strikingly increased, although its side effects became more intense. The xanthine drugs, such as theophylline, were tolerated in larger quantities than usual. With the restoration of an improved dietary, the patients showed a gradual return to their previous status. (Parenthetically, cases of psychogenic asthma

reacted similarly, being better during the period of military stress, but relapsing gradually after the re-establishment of quiet.) Probably not unrelated to Gutmann's observations is the maxim of Lindsay (1923) recently quoted by Babey[11] among other aphorisms concerning the broncho-pulmonary system: "The asthmatic should go supperless to bed."

Among the specific foods which have been the subject of recent reports are field beans,[235] grape products,[43] and cottonseed.[210] In India, according to Sadasivan and his colleagues,[235] field beans (*Dolichos lablab*), also known as hyacinth beans, a staple of the Indian diet, and house dust are the principal allergens causing asthma. Other legumes, molds, eggs, tea and milk are also considered important. Desensitization with field bean extract was effective and, surprisingly, brought about a reversal of the positive intradermal skin tests. Such reports once again point up the necessity of considering the "allergens peculiar to the part of the world we live in. . . ." The patient described by E. A. Brown[43] was a Catholic priest whose liturgical duties required the ingestion of grape wine, with resulting coryza, cough, bronchospasm and urticaria. Marked skin and positive passive transfer reactions were produced by grape, grape seed and commercial grape juice. Oral desensitization with grape juice failed, since symptoms recurred when the dose reached fifty drops of a 1:100 dilution. Limitation of the ingestion of wine to five drops once daily still gave rise to symptoms, although they were milder. In response to a query,[210] it was again indicated that in the vast majority of instances of cottonseed sensitivity, the oil can be tolerated with impunity. (This reviewer must interpolate, however, that sensitivity to the ingestion of cottonseed oil products does occur.) A positive reaction to cottonseed should interdict foods containing cottonseed meal, such as certain health breads, as well as the inhalation of dust from cotton linters. Desensitization with cottonseed antigen is a hazardous procedure and seldom indicated, because of the extreme antigenicity of cottonseed.

Rowe and Rowe[230] have reiterated their experience minimizing infection or bacterial allergy as a common cause of bronchial and nasal allergy. They emphasize the approximately equal roles of food and inhalant allergies with minimal bacterial allergy in asthma in all age groups. The failure to recognize the frequency and importance of food allergy stems from the frequency of negative skin reactions to foods, dependence on diets made up of foods to which skin tests are negative, and on insufficient use of the cereal-free elimination diet. Food allergy is thought to cause most of the recurring attacks of bronchial asthma in childhood, usually starting with nasal symptoms, often with fever due to such allergy rather than to infection, and followed in hours or one or two days by asthma. That allergy to bacteria rarely causes asthma is also supported by the occurrence of infectious colds and bronchitis without activation of asthma when causative food or inhalant allergies are controlled. The results so achieved have also reduced oral and nasal surgery to a minimum in their experience.

Infections.—Other observers have disagreed with the viewpoints outlined just above, feeling that nasobronchial infection is a major cause of asthma. On the basis of fever, leukocyte and differential counts, roentgenograms, sputum examination both grossly and in the laboratory, physical examination, and clinical course, Dannenberg[67] determined that 69.5 per cent of asthmatic patients requiring hospitalization for asthma showed evidence of respiratory tract infection. In view of the monthly curves

of asthmatic fatalities in England and also their parallelism with the death rate from bronchitis, as outlined above under the heading of "Incidence and Mortality," Williams[292] concluded that infection is a dominant factor in the etiology of deaths from status asthmaticus.

Stevens[266] studied the relationship of asthma to infectious colds in children. Nine patients between one and three years of age, who appeared sensitive only to bacteria and who were treated with polyvalent bacterial filtrates, were followed for four to five years. In cases of infectional bacterial asthma occurring with common epidemic colds, monthly testing with the nucleoproteins of the common upper respiratory bacteria gave evidence of fluctuating sensitivity; the number and severity of positive reactions decreased between April and August. The severity of the asthmatic attacks, the incidence of the respiratory pathogenic bacteria recovered during infections, and the intensity and frequency of positive dermal reactions were found to parallel each other. A stock mixture of filtrates from selected strains of hemolytic streptococcus, *Streptococcus viridans*, *Neisseria catarrhalis*, *Hemophilus influenzae*, pneumococcus II, and *Staphylococcus aureus*, sometimes with autogenous filtrates either substituted or added, was employed in treatment. Favorable results were obtained. These children appear to be focally hypersensitive to bacteria causing the second stage of a cold, and asthmatic attacks occur only with colds in the winter, not in the summer.

In a different group of seven children, three to nine years of age, who were sensitive to ragweed and a few other allergens, it appeared that the virus or bacteria complicating a cold may cause an asthmatic attack even though the respiratory membranes are not specifically sensitized to bacteria. The irritation of the inflammation occurring with the cold, when superimposed on a pre-existing frank or latent bronchiolitis, will cause an asthmatic episode even in the absence of bacterial sensitivity. The treatment of the underlying allergy is adequate in these patients. If asthma occurs with colds during the summer, pollen sensitization should be suspected, but if there is sensitivity to ragweed, asthma may occur with colds until early winter.

Even *Bacillus coli* may cause infectious asthma, according to Sacca.[234] The sputum yielded an almost pure culture in his case, and a large immediate reaction was obtained on intradermal testing with an autogenous vaccine containing fifty million organisms per ml. Therapy with the vaccine along with streptomycin, potassium iodide, and ACTH was successful.

Tuberculosis is not an important etiologic factor in the production of asthma, according to the results of a study of 1,190 asthmatic patients by Fuchs.[104] Only twenty-seven cases (or 2.3 per cent) showed roentgen evidence of pulmonary tuberculosis. Of these, eleven had true allergic asthma, ten had infectious (bacterial) asthma, and six had nonallergic or "false" asthma. In ten of the eleven cases of "true" asthma, the disease preceded the appearance of tuberculosis. Tuberculosis in asthmatics makes the prognosis grave.

The other side of the relationship between infection and asthma is discussed by Fries and Borne;[103] a temporary clearing of intractable allergic symptoms may result from an acute intercurrent infection. The phenomenon was observed in eleven asthmatic children, of whom four also had concomitant atopic dermatitis, and in five other pediatric allergic cases. All had had severe allergic manifestations for prolonged periods of time. In the majority, the intercurrent infection was measles; in others, pneu-

monia or tonsillitis. In several instances, the remission of the allergic disease was dramatic and where two allergic states coexisted, both behaved similarly. The "anergic" phase usually became apparent at the height of the febrile period and continued for from five days to one year, lasting in most cases for a few weeks. Another group demonstrated allergic remissions during infection with vaccinia virus (Kaposi's varicelliform eruption) but were not followed after discharge from the hospital. Unfortunately, there is no regularity of beneficial effect of fever or infection on the allergic state. On the contrary, with infections accompanied by slight elevation of temperature an adverse effect is more frequently seen. The explanation of the improvement, when it occurs, may lie in a mobilization of the endocrine defense mechanisms during fever, or possibly in increased histaminolytic activity.

Bronchiectasis.—Opinions continue to differ regarding the occurrence of bronchiectasis in asthmatic patients. Overholt[196] has answered the critics of his report regarding the association of the two conditions by pointing to semantic problems, but emphasizing that all the patients in his series had been previously diagnosed and treated for asthma, and certainly had paroxysmal dyspnea and wheezing. In an additional report[197] adding three cases, he concluded that asthmatic patients apparently have a high incidence of bronchiectasis, either as a complication of or an etiologic factor in the asthma. Bronchiectasis should always be suspected in cases of intractable bronchospasm, and proper treatment of the former yields good results for the latter.

On the other hand, Westermark and Wiholm[290] of Stockholm reported that the association of the two conditions was comparatively rare. Bronchographic examination of 100 consecutive patients with bronchial asthma, mostly of long standing, revealed bronchiectasis in only four instances, and in each of these the lesion was relatively minimal.

Drugs.—In a compendium of allergenic drugs, E. A. Brown[42] lists the drugs most frequently associated with bronchospasm: acacia, acetylsalicylic acid, ACTH, anesthetic agents, antihistaminic agents, argyrol, the arsenicals, atophan, atropine, asthma powders, cocaine, cortisone, derris root, demerol, digitalis, emetine, heparin, insulin, iodides, ipecac, karaya gum, liver extract, lycopodium, the mercurials, morphine, pantopon, para-aminosalicylic acid, penicillin, pollen extracts, privine, piromen, sera, streptomycin, sulfonamides, takadiastase, tannic acid, tetraethylammonium bromide, thiamine, and vaccines.

Endocrine Allergy.—The investigations of Solari, Ruiz Moreno and and Fernández[259] tended in part to confirm the earlier observations of Zondek and Bromberg on endocrine allergy, but they prefer to use the term "hormonal allergy." Intradermal tests were performed on asthmatic and other allergic females in the ages of sexual hormone activity whose symptoms exacerbated before or during menstruation; separate tests were done with the vehicles, oil of sunflower, peanut oil, and olive oil, and with estradiol dipropionate, progesterone, and testosterone propionate dissolved in each of the oils. The authors hypothesize that endocrine allergy is really exogenous, caused by substances chemically related to the hormones. Allergization could result from the ingestion or injection of steroidal substances. Subsequently, the hormones appearing cyclically in

the blood would, on exceeding a certain threshold level, provoke the allergic reaction because of their chemical similarity. In some instances, "paradoxical reactions" occurred with the pure oily vehicle, not containing any steroid hormone. Treatment was carried out with the steroid or steroids and/or the proper oil giving rise to "recurrent" reactions occurring forty-eight hours after the test. Apparent improvement or "cure" followed in most of the cases so treated.

Cardiospasm.—According to Andersen, Holman and Olsen[5] asthma may occasionally complicate the course of cardiospasm. Among 601 cases of cardiospasm encountered at the Mayo Clinic, one had typical bronchial asthma with a normal roentgenogram of the thorax, three others had experienced typical asthmatic episodes associated with pneumonitis, and two had emphysema. All four patients noted the onset of asthma after the symptoms of cardiospasm. It is assumed that bronchospasm sufficient to cause wheezing results from the tracheobronchitis caused by repeated aspiration of small amounts of esophageal contents. Successful treatment of cardiospasm by hydrostatic dilation of the esophagogastric junction resulted in improvement of asthma in two of the patients. It should be noted that other pulmonary complications of cardiospasm, particularly aspiration pneumonitis, occur more frequently than asthma.

PSYCHOSOMATIC FACTORS

Numerous reports in the past year dealt with the psychodynamics of bronchial asthma and its psychotherapy. The various approaches employed included study of the mother-child relationship, evaluation of the emotions and situations precipitating paroxysms, informal psychotherapy and hypnosis, investigation of the effect of emotions on respiration and on arterial oxygen saturation, and analysis of the interrelationship between asthma and psychosis.

Evaluation of the mother-child relationship in twenty-two allergic children including twelve with asthma convinced Mitchell and her colleagues[188] that a combination of allergic and emotional factors were responsible for the allergic symptoms. The emotional factors can usually be easily observed and demonstrated; their recognition and treatment may lead to more satisfying results. The direct psychiatric approach to these patients was found to be difficult and often unrewarding. A co-operative effort of a medical social worker, psychologist, psychiatrist, allergist and pediatrician was the most helpful. With the exception of two, none of the children showed clinical signs of overt gross psychological disturbances. The mothers were found to be relatively and absolutely strong, active, and anxious, with a great need to be in psychologic "control." Many of the children were born outstandingly early or late in the mother's childbearing period and so occupied a position of particular importance to the mother. There was a periodic oscillation of the mother's attitude toward the child, changing from extreme concern and overprotection to one of intolerant and impatient annoyance—this may help to explain the periodic nature of allergic manifestations. Children of both sexes showed much stronger identification with the mother than with the father, and displayed great ungratified dependency needs. The allergist or pediatrician is in an advantageous position to supply emotional support and insight with his therapy; only the exceptional case requires handling by a psychiatric specialist. Sirmay[255] also recommends informal psychotherapy

during the course of desensitization, unless progress is not satisfactory. He believes that maternal rejection, induced by the expense, family sacrifices, and increased effort incident to the disease, is the result rather than the cause of asthma. The objection to the maternal rejection theory raised by Bowen[37] on the basis of his observations on twins has been alluded to under the heading of "Heredity."

In a psychiatric investigation of thirteen adult and seven pediatric cases, O'Neill[195] observed that asthma first appeared in children either when the patient was the sole child in the family or shortly after the birth of the next sibling; and in most adults, at the time of an intense emotional experience. In both adults and children, emotional tension—mainly anxiety, resentment and guilt—was by far the most important precipitant of attacks. He holds the objection that asthma cannot be psychogenic when beginning in early childhood to be invalid, since never again in life are emotions so intense and overwhelming. Psychotherapy, with no other treatment except the use of a nebulizer when necessary, led to recovery or great improvement in nine cases, improvement in seven, of which three subsequently relapsed, and no change in four. In pediatric cases, the mother was accorded as much or even more attention than the child in an effort to modify her morbid attitudes such as overconcern or irritability masking real anger.

In the psychiatric examination of fifty patients referred to him, Leigh[158] found evidence of multiple psychosomatic factors: (1) sudden intense emotion precipitating attacks; (2) the significance of crying [or laughing] in starting or stopping attacks; (3) sexual conflicts; (4) disturbance, or threat of disturbance, of a dependent relationship; (5) psychic identification on the part of the patient with the dyspneic attacks of other individuals; and (6) desire for attention or so-called psychic "gains." Of all these, by far the most important was the influence of sudden intense emotion, most commonly anger, and in particular, inhibited anger.

Boulanger[36] submitted nine adult asthmatics to Rorschach and Szondi tests. The results did not indicate neurosis or psychosis, but all exhibited maternal fixation, anxiety, repressed aggressiveness and an immense desire for affection. These findings are thought to differ from those in neurotics whose conflicts express themselves symbolically. The asthmatic subjects manifested extreme emotional dependency, particularly in relation to their mothers, with resultant vulnerability to the emotion of frustration. They overcome their emotional insecurity by aggressiveness which is repressed for moral reasons. The asthmatic paroxysm, accordingly, takes the form of an outgrown type of expression. However, according to Boulanger, we cannot pretend to explain the entire pathogenesis of so complex a disease as asthma by a psychologic interpretation, nor can other diverse causes be excluded.

According to Grace and Graham,[115] a certain specific "attitude" and its associated physiological changes are characteristic of each of several syndromes and diseases occurring as responses to life situations. Asthma occurs in association with the same attitudes as vasomotor rhinitis, the individual facing a situation with the wish that he didn't have to do anything about it, or that it would go away, or that somebody else would take over the responsibility. Typical statements regarding the patient's attitude toward the situation precipitating asthmatic paroxysms were: "I wanted them to go away." "I just couldn't face it."

Fagerberg[89] found the "premorbid personality" to be abnormal in most

of thirteen asthmatics, and that in about half, emotional conflicts antedated the onset of asthma. In the opinions of nearly all the patients, everyday "nervousness" had an adverse effect on the disease. As a psychotherapeutic experiment, four patients were given injections of physiologic saline solution, but were told it was ACTH. There was dramatic subjective improvement, but rhonchi and expectoration continued until ACTH was substituted. Magonet[175] employed hypnosis and posthypnotic suggestion along with reassurance, re-education and guidance, since asthma was considered by him to be a respiratory neurosis with alterations in respiration as a physiologic accompaniment of emotional disturbances. Semihypnosis induced by the repeated playing of a phonograph record containing an appropriate formula of relaxing words and loaned to the asthmatic patient has proved useful to Morwood.[190]

Miller and Baruch[184] observed that the emotional disturbances underlying asthma fall into four areas: (1) of prime importance in setting off attacks is the patient's hunger for affection, although often hidden behind a façade of bravado or aggressiveness; he feels dependent and clinging, irrespective of age; (2) fear that the emotional support he craves will not be forthcoming or that he will lose what he has; the fear, either actual or in fantasy, of maternal or mother-image rejection; (3) hidden anger, although he may appear compliant and reasonable; and (4) anxiety over exposing his anger, with attendant repression. His anger is turned inward against his own person. Accordingly, the four major psychotherapeutic tasks in the management of acute attacks are: (1) to feed the patient's affected hunger; (2) to lessen his fear of rejection; (3) to reduce the anxiety blocking the expression and even the awareness of the anger within him; and (4) to help him release his anger without harm to others or to himself. These aims are not accomplished at once—rather in a well-defined sequence. Hostility may be vented against the doctor as well as against others. The doctor, and even his assistants, may continue to lend emotional support along with the medical treatment.

Three studies were concerned with the influence of emotions on the respiration of asthmatic patients. Deutsch[73] pointed out that the unconscious can use the striated respiratory muscles for the expression of emotion, thereby changing the individual's characteristic respiratory pattern. The ego of the asthma patient is unable to appease the conflicts between psychic symptoms. This leads to disorganized respiratory behavior on account of ego panic, possibly culminating in an asthmatic attack. The respiratory muscle apparatus is said to be "psychologically sensitized." The asthma attack does not represent only a suppressed cry for the mother or a fear of separation from her, but is a symptom complex expressing the panic of the ego in the face of the demands of irreconcilable instinctual forces competing for supremacy. In pneumographic tracings on fifteen asthmatic patients, Stevenson and Ripley[267] observed changes in the rate and depth of respiration, and in the inspiratory/expiratory ratio relating to their prevailing emotional states as altered by directed discussions. An increase in the rate and/or depth of respiration and sighing occurred chiefly with anxiety, but sometimes during anger and resentment. A decrease occurred when the subjects were tense and on guard, or when sad or dejected. Irregularity of respiration was commonly associated with anger, especially when repressed; also with feelings of guilt and with weeping. Prolongation of expiration during periods of emotional disturbance was found in a higher proportion of patients with asthma than

of those with anxiety; sometimes wheezing and dyspnea ensued. Respiratory symptoms associated with emotional disturbances may result from altered respiratory function in response to symbolic stimuli to action and often are related to conflict concerning such action.

In an intensive investigation of thirty cases, Doust and Leigh[75] employed oximetric determinations to follow the arterial oxygen saturation and the "efficiency score" during the evocation of emotionally stimulating material, by means of directed interviews and the introduction of visual material—the "controlled stress test." Twenty-five of the patients showed neurotic or psychotic symptoms. In nearly 90 per cent the predominant mood was one of depression, although it was difficult to decide whether this was a reaction to a long-standing illness or perhaps closely associated with the asthma or occurring as a temporal alternate to it. Pent-up emotional tension was accompanied by anoxemia. The anoxemia was sometimes inhibited (not increased!) in suitably predisposed subjects by the occurrence of asthmatic dyspnea. Evocation of depression or rage at the psychiatric interview or induced by discussion of significant interpersonal relationships produced measurable degrees of anoxemia. Simulated asthmatoid breathing actually increased arterial oxygen saturation levels. The anoxemia accompanying emotional tension could be overcome by means of motor expression of the emotion, such as weeping, laughing, the acting out of anger, or confession—and, surprisingly, by asthma.

Opinions still differ regarding the interrelationship of asthma and psychosis. Sabath and Luce[232] studied thirty-two, and Leigh and Doust[159] twenty-eight psychotic patients with asthma. The former investigators found co-existence of the two conditions in nineteen cases, antagonism (clearing of asthma during overt psychosis and reappearance during remission of the psychosis) in eleven cases, and occasionally both relationships in the same patient, depending on the level of the psychosis. There was no selective distribution of asthma among the psychiatric diagnostic categories. However, asthma was of the "co-existent" type in all paranoid reaction types of psychosis. Whether the psychotic retains or loses his asthma appeared to be directly related to the extent of his break with reality—the "depth" of his psychosis. Those who retained their asthma had less break with reality and more intact personalities. On the other hand, Leigh and Doust[159] deny a dynamic interrelationship between psychosis and asthma. In their series, only two instances of alternation between psychosis and asthma appeared, and more careful observation left even these open to doubt. There was no evidence that any particular psychotic constellation was associated with attacks of asthma; in fact, a variety of different stimuli were capable of evoking paroxysms. In about two-thirds of the group, asthma had been present for more than ten years, but the psychosis for less than five years. In one mental hospital only sixteen asthmatics were found among 2,400 patients, an incidence of 0.64 per cent, as compared with 1.5 to 2 per cent in the general population.

EXPERIMENTAL ASTHMA

It is generally agreed that the procedures or remedies, including cortisone and ACTH, which relieve asthma in man do not inhibit anaphylaxis in animals. To study this further, Feinberg et al[94] devised a method of producing asthma of controllable degree in guinea pigs. The animals were passively sensitized by the intravenous injection of guinea pig antiovalbumin serum in varying amounts. Inhalation of aerosolized solution of

crystallized ovalbumin forty-eight hours later produced unquestionable signs of asthma. This permitted evaluation of various protective and stress factors by comparing in control and treated groups the length of time that the aerosol was tolerated before the appearance of asthmatic manifestations and the proportion of animals tolerating ten minutes of exposure. Significant protection was afforded by parenteral pretreatment with each of the following: tripelennamine (Pyribenzamine®), cortisone, ACTH, localized chemical inflammation produced by an intramuscular injection of an antimony compound, yeast suspension, sodium nucleate, and human serum. A pyrogenic bacterial polysaccharide (Piromen®) had no significant effect. The surprising results with human serum recall the old autohemotherapy of asthma. In a separate study relating to pretreatment with 50 mg of cortisone eighteen hours before the challenging aerosol exposure, Feinberg and Malkiel[93] reported that in a significant percentage of guinea pigs cortisone was effective in inhibiting or delaying the symptoms of asthma.

Ratner[220,221] investigated individual differences in guinea pigs, and temporal and quantitative factors influencing the development of experimental asthma. The animals were sensitized by repeated inhalation of dry horse dander in a natural manner for varying lengths of time and subsequently challenged by re-exposure on varying schedules at differing intervals. While the resulting symptom complex was originally called "respiratory anaphylaxis," it is believed to be sufficiently analagous to human asthma to be properly termed "experimental asthma." Ratner found that the duration of exposure and certain time factors played an important part, plus, perhaps, certain inherent attributes of individual animals. With increasing exposures, sensitization became established more rapidly. Beyond a certain optimal amount of exposure, there was no regular increase in sensitization, but rather the reverse. Although innate differences in susceptibility and resistance were found (about seven per cent appeared to be resistant), it is not possible to say whether resistance is relative or absolute, nor whether it can be explained on the basis of heredity. An extensive breeding program might shed light on this question. Certainly, under optimal conditions, experimental asthma can be induced in the majority of guinea pigs.

PULMONARY FUNCTION TESTS AND RESPIRATORY PHYSIOLOGY

Attempts to achieve simple but informative tests of pulmonary function were reported. Alexander and Reydman[3] devised a test for evaluating the efficiency of pulmonary gas exchange, employing an earpiece oximeter and a basal metabolism apparatus. After rendering the patient hypoxic (arterial oxygen saturation of 80 per cent) by rebreathing into an air-filled spirometer, they determined the time required for the oxygen saturation to rise from 80 to 90 per cent while the subject was breathing room air. The normal value for resaturation time was 13.4 ± 3.4 seconds. Segal and his colleagues[249] described a simple ruler-graph to be applied to single tracings of the recorded vital capacity, permitting rapid calculation of the volume of air ejected in each second of the vital capacity. The results compared favorably with devices employing a mechanical solenoid timing mechanism but also gave additional data. The method was thought to be useful in assessing the relative efficacy of bronchodilator preparations in relieving bronchospasm.

Gross[118] suggested a new "respiratory index" to detect the

occurrence and severity of dyspnea. The respiratory index= vital capacity in cc.

$$\frac{\text{vital capacity in cc.}}{100} + \text{breath-holding time in seconds.}$$

Subjects with normal cardiorespiratory function averaged 100 (range 71 to 160). Values below 60 were invariably associated with dyspnea and in general, there was a parallelism between the severity of the dyspnea and the decrease in the index. In ten cases of asthma with severe dyspnea, the respiratory index reached very low figures (21 to 36) and as a group gave values lower than decompensated cardiacs with intense dyspnea. The index seemed to give more information than its component parts, Gross feeling that the vital capacity more closely reflects the somatic and the breath-holding time, the neuropsychical factors involved in dyspnea.

A modification of the vital capacity technique was employed by Leslie,[160] comparing the magnitude and contour of inspiratory and expiratory vital capacity recordings. The expiratory capacity is performed in the usual way, but the inspiratory capacity measures the amount of air inhaled maximally after a complete exhalation. In cases of pulmonary emphysema, the expiratory vital capacity was less than the inspiratory, and the expiratory curve was consistently slower than the inspiratory. Normal subjects did not give these findings. The method was stated to reflect closely the clinical condition of patients with impairment of expiration.

Dulfano et al[77] studied the first-second vital capacity and its ratio to the total vital capacity, employing a spirometer with an electric timer attachment. Asthmatic patients in the symptom-free stage gave ratios ranging from 31.6 to 75.8 per cent as compared to accepted normal values of 75 to 85 per cent. There was no significant change in the ratio after administration of a bronchodilator aerosol, and this was also true during acute exacerbations or spontaneous attacks, although the absolute values for both the first-second and total vital capacities were increased considerably. These findings were interpreted as representing a fixed state of the bronchial tree—at least in those patients who have had bronchial asthma for many years. A decreased ratio of first-second vital capacity to total vital capacity, in the presence of a markedly diminished total vital capacity, is a definite indication of the presence of obstructive ventilatory insufficiency. However, the ratio of first-second to total vital capacity, considered alone, does not accurately reflect the degree of improvement of the asthmatic patient under treatment. Lowell and Schiller[168] found that the rate of change in the speed of expiration of air changes (i.e., slows) at a constant or almost constant rate in normal subjects, but may vary during a single expiratory effort in patients with chronic lung disease because of poorly understood intrapulmonary factors. Accordingly, in some patients with pulmonary disease, no single measurement or index derived from the timed vital capacity (including the determination of the volume expired in the first second) can be regarded as truly representing the manner in which air is expired from the lungs. Studies on the effect of isopropylarterenol aerosol in an asthmatic patient before and after cortisone therapy and on an attack induced by penicillin aerosol in a penicillin-sensitive patient confirmed these conclusions.

According to Bachmann and his co-workers,[13] spirographic tracings between attacks revealed the delayed expiratory sign (DES) in most asthmatic patients. It was more likely to be present when the asthma was associated with or complicated by bronchial infection. It also occurred in

non-asthmatic pulmonary disease, such as bronchiectasis, fibrosis, and emphysema, and even in a few normal subjects. Administration of a nebulized epinephrine derivative decreased the DES in most cases of purely allergic asthma, although the vital capacity did not always improve; in cases with bronchial infection, the DES decreased less or not at all after aerosol therapy. These findings are interpreted as indicating that the bronchial obstruction is due to spasm or mucosal edema and congestion in the former group, but is due in the latter group to pulmonary emphysema or serious disorders of the bronchial musoca with chronic infiltration. The DES often disappeared in actual asthmatic attacks, whether spontaneous or induced. Repetition of the studies after some time of therapy showed decrease of the DES in purely allergic asthmas, with or without co-existing bronchial infection, but slightly or not at all, despite subjective improvement, in unclassified asthmatics with bronchial infection [presumably infectious asthma] or in the non-asthmatic chronic respiratory conditions. It is concluded that the DES indicates transient or permanent bronchial obstruction or a diminution of pulmonary elasticity. However, a decrease or disappearance of the DES after nebulization with an epinephrine derivative or at a later time in the course of the disease after treatment, indicates that the bronchopulmonary disorder is not irreversible.

McKee[179] evaluated the ventilatory function tests in asthma and other lung diseases. In seven asthmatics, the total lung capacity was slightly greater than the predicted normal in most instances. The maximum breathing capacity (MBC) was low in all cases. The breathing reserve ratio

$$\left(= \frac{\text{MBC} - \text{minute volume}}{\text{MBC}} \right)$$

ranged from 56 to 84; dyspnea usually occurs when this ratio is below 60 or 70. The reserve volume/total volume ratio was definitely elevated in all cases, ranging from 37 to 61 per cent, values over 35 per cent being abnormal. The index of intrapulmonary mixing was normal in all but one case. His investigations convinced McKee that ventilatory tests do not usually give a completely adequate evaluation of pulmonary function and are of little assistance in defining the pulmonary disorder of the patient. But, since they are objective and reasonably reproducible in an individual case, they are of great value in following patients for comparative information and also in assessing the efficacy of drugs in improving lung function.

Lowell and others[171] employed the Millikan oximeter to determine the rate at which the blood of asthmatic subjects, purposely rendered hypoxic by the inhalation of 10 per cent oxygen, became saturated upon breathing 100 per cent oxygen. In fifteen patients with asthma, emphysema or both, four to twenty seconds was required for the arterial saturation to rise from 90 to 95 per cent, while in normal subjects the time was consistently less than six seconds. Those patients with the most marked respiratory disability required the longer periods—especially those with emphysema. In two cases, there was a lack of correlation between the minute volume and the resaturation time, which was readily influenced by altering the degree of asthma by means of subcutaneous epinephrine or histamine aerosol. A reduction in the minute volume which may be transient commonly occurs during induced asthmatic attacks. Uneven distribution of inspired gas is also known to be present in asthma complicated with

varying degrees of emphysema, but the contribution made by asthma alone to this abnormality remains to be determined. It would appear that spontaneous asthma of minimal degree and induced attacks, even without more than moderate respiratory discomfort, entail a measurable decrease in pulmonary efficiency. Although the increased respiratory effort during asthma may bring about an apparently adequate minute volume, it may not be sufficient to compensate for changes in the lungs interfering with gaseous exchange. This may explain the common discrepancy between the degree of the patient's discomfort and the apparent adequacy of ventilation as judged by bedside observation.

Other pertinent physiologic studies with reference to emphysema will be mentioned below under the heading of "Complications."

In summary, one cannot but be impressed with the ingenuity and sedulousness of the investigations into the pathophysiology of bronchial asthma. As information accumulates, our understanding will be heightened. However, the complexity of existing methods and the divergent opinions of the interpretations leave us a long way from everyday clinical application of such approaches.

DIAGNOSIS

Every physician is aware of the difficulties of establishing objective evidence of asthma when the patient is examined between attacks. Gutman[121] has found that residual signs can be most often discovered by auscultation of the supraclavicular fossae bilaterally, particularly in the angle between the clavicle and the medial head of the sternocleidomastoid muscle at the manubrium sterni. Here the last residual evidence of prolonged expiration and the characteristic bronchial asthmatic breath sounds can be detected, often at a time when they are no longer audible elsewhere in the chest. This area has consequently been designated by him as the angulus asthmaticus or the asthma auscultation point. He warns against drawing conclusions from the presence of expiratory prolongation over the right apex only, for anatomic reasons. The earlier methods of bringing out abnormal sounds during examination, such as forced respiration, exhaling against pressure, thoracic compression, or cough, are briefly reviewed.

Hamblen-Thomas[126] discussed the value of bronchoscopy in the diagnosis of asthma. Bronchoscopy should be done in doubtful cases, being helpful in differential diagnosis, and also to assess the patient's progress in some instances.

DIFFERENTIAL DIAGNOSIS

A variety of case reports and clinical investigations of conditions simulating the wheezing and dyspnea of bronchial asthma appeared in the past year. Unger[279,281] discussed the differential diagnosis with special reference to the upper respiratory tract. In the pediatric field, Logan[166] offers the following list for differentiation: (1) "rattle" in the throat due to excessive saliva or mucus; (2) acute laryngotracheobronchitis; (3) foreign body in the bronchial tree; (4) bronchiectasis; (5) lymphadenopathy, most commonly at the bifurcation of the trachea; (6) cystic fibrosis of the pancreas; (7) relaxed larynx; (8) mediastinal tumor, including Hodgkin's disease; (9) retropharyngeal abscess; (10) pertussis; (11) dust bronchitis; (12) sighing dyspnea; and (13) anomalies of the great vessels at the base of the heart. The list presented by Criep[61] differs

somewhat: pancreatic fibrosis, congenital laryngeal stridor, enlarged tracheobronchial lymph glands, croup, tracheobronchitis, pulmonary tuberculosis, Löffler's syndrome, foreign bodies in the lung, and occasionally pulmonary malignancy. Although some have thought that an enlarged thymus may produce asthma, Criep believes that it is more likely to be a manifestation of the general acute allergic state.

At the other age extreme, asthma may not infrequently begin late in life, according to Rosenberry[229] and a careful history may reveal some evidence of allergy in earlier years. The diagnosis of allergic asthma becomes increasingly difficult as age advances, and differential diseases to be considered include forms of bronchitis, foreign body, mediastinal tumors, primary and secondary pulmonary neoplasms, emphysema, pneumoconiosis, and so-called cardiac asthma.

Unger[280] pointed out that "nonallergic asthma" can occur from any condition in which there is partial obstruction of the laryngotracheobronchial tree, and also from sudden dilation of the left ventricle. He presented patients whose asthmatoid symptoms were due to a leiomyoma of the trachea, carcinoma of the carina, substernal goiter, silicosis of the lungs, acute cardiac dyspnea and bronchiectasis. Large numbers of eosinophils were found in the sputum of the patients with carcinoma and silicosis. He urged all allergists to become better diagnosticians and all internists to learn more about allergy. "Nonallergic asthma" is uncommon, and of the cases suggestive of asthma, probably 90 per cent had true bronchial asthma. In discussion, Epstein[88] declared that this may be true in an allergy clinic, but not in his experience in a chest clinic where the majority of patients over forty years of age complaining of wheezing were found to be suffering from chronic bronchitis, bronchiectasis and obstructive emphysema. He described asthmatic symptoms occurring in cases of tuberculous ulcerative endobronchitis with tuberculous pneumonia and of Friedländer's bacillus infection with diffuse fibrosis of the lungs. An anonymous article[4] reported necropsy findings of gross bilateral fibrocaseous pulmonary tuberculosis with rupture of a large bulla causing extensive pneumothorax in a man who had a sudden severe "asthmatic" episode. Another patient, aged sixty, with a history of childhood asthma, had had for about one year, typical nocturnal asthmatic seizures alleviated by ephedrine and by epinephrine nebulization; death occurred in a dyspneic paroxysm and autopsy revealed carcinoma of the left lower lobe bronchus with extensive metastases. Asthma occurring in a middle-aged person can be aggravated by silicosis, and silicosis may induce bronchospasm secondarily in some individuals, according to the answer to a query.[214]

Boesen[33] investigated the asthmatic proclivity of children with asthmatic bronchitis. The differentiation is admittedly difficult, especially in older children, and is based largely on analysis of the symptomatology. The statistical probability of the onset of asthma in later life appeared to increase with the age of the patient with asthmatic bronchitis and also when the family history was positive for allergy. Less than 10 per cent of cases under one year old developed asthma; over one year of age, but without a family history of allergy, about 30 per cent did so; but the figure was 70 per cent for bronchitic children over three years of age and with a positive family history. A blood eosinophilia (over 400 per cu mm) during the bronchitis indicated a poorer prognosis as regarded the eventual development of asthma than did its absence. The presence or absence of fever, and the sex of the patient did not influence the outcome. The

likelihood of subsequent asthma was less when the bronchitis was complicated by pneumonia.

A condition known as "farmer's lung" or "thresher's lung" appears to result from the inhalation of dust from mouldy hay or straw. Fuller[105] observed thirty-two cases in eight years: five had acute isolated attacks and showed fine alveolar mottling on roentgenograms; twenty-four were in the subacute stage; and three had chronic pulmonary changes (including emphysema and scattered fibrosis) occurring after repeated prolonged exposure. There is no conclusive evidence that the disorder is a true bronchomycosis due to *Candida albicans* or other fungus, or that it results from bacterial infection. A third possibility, that it is an asthmatic response to sensitization to degradation products of moldy grass or to the molds themselves, is not convincing in view of the absence of forced expiratory effort and of sibilant rhonchi. A final possibility is that of irritation of the bronchial epithelium by the breakdown products of mold spores or possibly grass particles, resulting in a miliary inflammatory response. Farmer's lung is almost never fatal, so necropsy material is not available.

According to Lewis,[163] hyperventilation syndromes, contrary to prevalent opinion, occur relatively frequently and are more likely to pursue a chronic, fluctuating course rather than one with brief, explosive attacks. They may arise from either organic or psychogenic mechanisms, or combinations of both. Patients with coronary, hypertensive or rheumatic heart disease, pulmonary emphysema, bronchial asthma and the Stokes-Adams syndrome are especially predisposed. The clinical manifestations are atypical, the respiratory ones generally being masked by prominent symptoms referable elsewhere, such as the neurovascular, muscular, cardiac, gastrointestinal or psychic systems. However, the respiratory disturbance, ranging from frequent sighing and yawning to gross hypernea, is quite evident to the examiner. The patients tend to exhibit a peculiar, heaving type of respiration involving the upper thorax and employing the accessory respiratory muscles. Fluoroscopy reveals a depressed, relatively immobile diaphragm.

One of the six cases reported by Lewis was a nurse hospitalized for an exacerbation of chronic intrinsic asthma. One week later, when much improved, she complained of thoracic tightness and within ten minutes developed generalized muscular twitching, clonic movements of the extremities, bloating, belching, tachycardia, dyspnea and disorientation. Diagnoses of hypertensive encephalopathy, coronary thrombosis and cerebrovascular accident were entertained, but the manifestations slowly subsided after administration of morphine. The next day during a discussion of the episode, she spontaneously staged a repeat performance typical of the hyperventilation syndrome; this quickly resolved when she rebreathed from a paper bag. The reviewer would interject that all allergists have had experience with the hyperventilation syndrome, and that the differentiation from asthma is relatively easy on observing the episode. We are indebted to Lewis, however, for emphasizing that it may complicate asthma, is often of chronic type, and is not infrequent. Hypoventilation is, of course, more likely to occur in asthma than is hyperventilation, as was recently reiterated in response to a query.[208]

A clinical entity called "smoker's respiratory syndrome" or "smoker's asthma" was described by Waldbott.[287,288] It is characterized by chronic pharyngitis (its most constant clinical feature), wheezing, dyspnea, cough

and expectoration, chest pain, precordial constriction, hoarseness, and a tendency to frequent respiratory infections. He observed fifty-eight patients, about half of whom recovered completely on cessation of smoking, while most of the remaining cases required antibiotic therapy in addition. A further group of eight cases with irreversible changes, previously diagnosed as "intrinsic" bronchial asthma or chronic emphysema of unknown origin, was thought to represent an end-result of the syndrome. They all had marked wheezing, dyspnea and cyanosis. Temporary benefit followed their discontinuance of smoking, plus therapy with antibiotics, cortisone and bronchoscopic lavage, but there was no long-range relief. In another eighteen cases, the syndrome was thought to complicate allergic asthma, and the latter could not be controlled until smoking was eliminated, in addition to other therapy.

Waldbott found the smoker's respiratory syndrome could be distinguished from allergic asthma in that the wheezing was not as distressing and was localized principally in the tracheobronchial region; the patients could sleep in recumbency, and they had no allergic changes or polyps in the nasal mucosa or sinuses, little reduction in vital capacity, no allergic background, no eosinophils in the blood or nasal and bronchial secretions, negative skin tests for tobacco and smoke, and no other sensitizations. The syndrome is very persistent and remissions rarely occur. Wheezing, cough and expectoration are most pronounced in the morning and not when the patient does most of his smoking. The mechanism is considered not to be allergic, but to involve chemical irritation and subsequent inflammation from such irritants as the nicotine, pyridine, collidine, ammonia, hydrocyanic acid and carbon monoxide present in tobacco smoke. The mucus leads to partial obstruction of the air passages and asthma-like wheezing. The possible bronchoconstrictive action of nicotine must also be considered. Exposure to such irritants as paint odors, burning wood, frying fat, or grain dust may also produce asthma-like wheezing in these patients. An editorial[84] emphasizes the importance of recognizing this condition in order to prevent subjecting the patient to unnecessary allergic testing or bronchography, and to remove the cause before advanced changes take place. E. E. Brown[45] is dubious about the syndrome, since fifty of his patients were not benefited by eschewing smoking and since the cough is not at its most severe when the patient inhales tobacco smoke.

Meakins,[180] an anonymous Note,[207] and Rackemann and Evans[219] discussed the differential diagnosis of asthma and heart disease. The last-named presented the clinical histories and autopsy findings of two cases in which myocardial infarction or pulmonary emboli occurred in asthmatic patients. Both received morphine shortly before the fatal terminations. Meakins[180] emphasized that the differentiation between bronchial asthma and paroxysmal cardiac dyspnea depends largely on evaluation of the symptoms and physical examination.

TREATMENT: GENERAL CONSIDERATIONS

The multiplicity of approaches and attitudes toward the therapy of bronchial asthma makes orderly discussion of the recent literature difficult. Some of the broader aspects will be reviewed here, and individual treatment measures will be considered in ensuing sections.

According to Herxheimer,[115] the treatment of asthma should encompass four aims: (1) Removal of bronchial irritability—possible only when a

single allergen is the sole factor causing the asthma. Such casual therapy is possible only in a small number of cases. (2) Elimination or counteraction of those stimuli which appear most harmful in the particular case—by employing sedatives, psychotherapy and, possibly, some of the actions of antihistaminics. (3) Removal of bronchial obstruction—by means of substances which relax the bronchial muscles, reduce mucous edema and remove mucus, such as sympathomimetic drugs, aminophylline, antihistamines and iodine compounds. (4) Improvement of air entry into the lung—measures improving ventilation. Breathing exercises accomplish this best in the chronic asthmatic with more inflation of the lungs than seems warranted by the degree of obstruction. The breathing difficulty is possibly caused by an "increased tonus" of the respiratory muscles and the diaphragm in such cases. The reviewer would take issue with the low estimate of cases calling for specific therapy and with the employment of antihistamines. The latter appear to be of limited value in a few instances of pollen asthma and some pediatric asthmatics, and then only with reservations.

The principles of the management of asthma has been discussed by Kallós,[152] Tillman,[274] Zolov,[294] Burrage and Irwin,[49] Buzzard,[51] Alexander,[2] and Criep.[63] In emphasizing the multiple and complex etiology of asthma, Buzzard[51] deplores the tendency to rely on a single "specialized" line of therapy, and extols the practice of patience, sympathy, understanding and encouragement. One could hardly disagree.

Criep[62] discussed the therapy of the asthmatic attack and of status asthmaticus. Among the methods cited, most of which are unobjectionable, exception must be taken to the mention of asthma powders containing stramonium and potassium nitrate, which most allergists believe have no place in modern therapy, and to the employment of 50 per cent sucrose intravenously, which is nephrotoxic, to accomplish tissue dehydration, when most cases of status asthmaticus are already in a state of dehydration.

Swineford[271] presented a list of fifty-one "Don'ts" in the treatment of asthma which cannot well be summarized, although one may be quoted: "*Don't be satisfied with good but incomplete relief from symptomatic remedies.* They do not postpone nor prevent the development of chronic asthma and its complications of chronic sinusitis, fibrosis, emphysema, chronic bronchitis, and ultimate chronic lung failure. Symptomatic remedies should supplement but should not replace specific therapy."

The treatment of status asthmaticus has been discussed by Segal et al,[247] Johnston,[148] and Pottenger and Krohn.[201] An anonymous author[263] holds that some cases do not need hospitalization, but such a decision must be considered by this reviewer as hazardous.

Among other items, Johnston[148] raises some interesting points in the therapy of status asthmaticus. He feels that epinephrine is being used too infrequently (he favors repeated 1 minim doses, leaving the needle in place), and that aminophylline, while a very useful drug, is being overused. For the epinephrine-fast case, he favors the hot water treatment suggested by Dr. Cazort: after receiving intravenous aminophylline, the patient drinks as many glasses of hot water as possible, at least one pint, and is encouraged to cough. He believes that "some severe asthmatics have been killed because of therapy with the antihistaminics" and this reviewer thinks that others would agree.

Pottenger and Krohn[201] base a rather unorthodox emergency therapy of asthma on the concepts that the patient is "deteriorating" as a result

of adrenal exhaustion, that the exhausted sympathetic nervous system defaults to the parasympathetic system, and that the swallowing of mucus and air dilates the stomach which presses against the diaphragm and reduces lung volume. Along with other therapeutic measures, they advocate the induction of emesis by ipecac, apomorphine or castor oil, attempts to improve diaphragmatic breathing by inverting children manually or raising the foot of the bed of adults, and the injection of crude adrenal cortical extract which is said to combat respiratory infections. Epinephrine is employed, but it is stated that sometimes 2 to 20 units of posterior pituitary extract is more effective. In the most severe cases, an intravenous drip is administered consisting of 1,000 ml of Ringer's lactate solution containing three parts per million of epinephrine, 500 to 1,000 dog units of crude adrenal cortical extract, 60 micrograms of vitamin B_{12} and 2 gms of calcium gluconate. Vitamin B_{12} is thought to extend the action of the adrenal cortical hormones, the crude form of which is stated to produce better results in the long run, though less rapidly so, than cortisone or ACTH, and calcium is considered to have a calming effect.

Hyposensitization therapy has its critics. According to Twort,[278] though many patients are convinced that they are greatly benefited, it is generally agreed that desensitization alone seldom meets with much success in the treatment of asthma, as opposed to hay fever. Nevertheless, he grants that if the results appear hopeful, repeated courses should logically be employed. Henriksen[134] in a follow-up study of a single "course" [duration not specified] of injections in 478 cases, found that the beneficial effect was considerably reduced after three years. Even after that length of time, however, desensitized patients were slightly better off than the controls, 59.8 per cent falling in the asymptomatic and improved categories, as compared to 52.4 per cent of 164 control patients treated without hyposensitization. In the three-year period, fourteen patients in the treated group and eight in the control group died of asthma. Henriksen observed that prolonged desensitization in several courses for a number of years seemed to improve the results. In response to a query,[211] the relative safety of permitting desensitization injections to be given by a nurse or technician in the absence of a physician was discussed and the question of legal liability raised. The cautious attitude expressed is commendable.

The question of migration for the relief of asthma was the subject of a recent editorial.[85] The results of climatic change are often disappointing. Although some migrant patients are improved they are few compared with those who are either not improved or made worse, and in some instances the apparent cure was the result of the concurrent application of some recognized measure, such as removal from pets, which could have been accomplished at home. The impetus for the editorial was the story of a family of six transported from Michigan to Arizona in a second-hand bus because of a flare-up in the asthma of a ten-year-old boy. The physician treating asthma should make every effort positively to identify the causative allergen in every case and to find a suitable treatment to be applied without a change of residence. In contemplating moving for reasons of health it is essential to determine whether the new climate will indeed effect an improvement and also whether the patient can live in the new community without being a ward of a local charity. Engelsher[87] adds that many allergy sufferers may acquire new sensitivity to the local pollens after moving. Belonje[25] of the Netherlands found that residence at the

seaside for periods of one year was beneficial for asthmatic children, and the improvement persisted after their return home. There was no significant correlation between their attacks and any meteorologic phenomenon, including solar flares, sun spots, cosmic radiation, atmospheric electrical charges, the passage of weather "fronts," disturbances of the magnetic field, direction of wind flow, and the degree of humidity.

It cannot be disputed that every effort toward the prophylaxis of asthma is justified. Glaser and his co-workers[109,110,111,149,172] have contributed a series of publications to this end. The gist of their thesis is that the gastrointestinal tract of the newborn is highly permeable to unaltered protein, and this is associated with "immunologic immaturity" of physiologic origin.[110] Therefore, the potentially allergic newborn child—one whose father, mother or sibling is allergic—is prone to become sensitized to milk, with its attendant chain of allergic consequences. They showed that a preparation of soy bean milk (Mull-Soy®) can be successfully used in over 85 per cent of cases to feed infants from birth, and is nutritionally adequate. In most instances, subsequent change to a cow's milk formula was made without difficulty. The withholding of cow's milk from the diet of potentially allergic infants for periods of six to nine months greatly reduced the incidence of subsequent asthma and other major allergic diseases, as compared to control groups from the same and from unrelated families.[149] Breast-feeding is permissible, and in some instances meat base formulas were used. The regime must be instituted from the moment of birth.[111] Certain foods such as eggs, beef, and wheat, are also interdicted until the period of immunologic inmaturity has passed. It is noteworthy that 80 per cent of infants with atopic dermatitis eventually developed asthma or some other respiratory allergy.[172] In outlining a broader program of asthma prophylaxis, Glaser[109] discussed the advantages of dietary control of the pregnant and lactating mother, the selection of cereals for the infant, the age at which egg should be started, the avoidance of dust, odors, allergenic bedding, toys, pets, insecticides, and drugs (especially aspirin and penicillin), the problems of routine immunizations, and even the subsequent choice of occupation. This article should be read by any one concerned with the prophylaxis of asthma, and certainly by all pediatricians.

Hill[136] pointed out editorially the hazards, particularly diarrhea and sore buttocks, frequently resulting from soybean feeding of the newborn infant. He felt that while allergy to milk is not uncommon, it is being overemphasized, and predicted that the procedure advocated by Glaser would not be widely used. Lowell and Schiller[169,170] voiced grave criticism of the selection of the experimental and the control groups in Glaser's studies and felt that the evidence did not support the concept of immunologic immaturity as a temporary phenomenon associated with the first year or two of life. Among other objections, they emphasized that the later appearance of sensitivity to cow's milk with major allergic disease occurred as frequently in the experimental group (though at a later age, as might be expected) as in the control groups. It is felt by them that the entire question remains open. Glaser and Johnstone[112] replied to these comments by granting that the experiment might not have accorded with ideal theoretical conditions, but denied that prejudices were allowed to affect the selection of cases. The importance of cow's milk allergy in infancy was emphasized. Discontinuation of soy bean feeding, because of diarrhea and/or irritation of the buttocks, intractable colic and emesis, was required in only 15 per cent of the cases.[109]

In closing this section, it is probably significant that no reports concerning the use of nitrogen mustard in the treatment of asthma appeared in the past year in the English language, nor, so far as available, in a foreign language.

TREATMENT: CORTICOTROPIN AND CORTISONE

Although no one gainsays the importance of cortisone and corticotropin as additions to our armamentarium, one senses in the voluminous literature an increasing emphasis on their limitations, on adherence to stricter indications, and on their potential dangers. Many authors administer antibiotics simultaneously with short courses of either hormone, with or without evidence of co-existing bronchial or other infection. Few fail to indicate that avoidance of allergens, hyposensitizing injections, and other therapeutic measures are essential for proper management (G. T. Brown[46]).

Andersson[7] found evidence of adrenal cortical hypofunction in a series of twenty-five cases: the average daily excretion of 17-ketosteroids was 5.65 mg, compared to a normal value of 9.13 mg, and of reducing corticoids was 0.52 mg, compared to a normal of 0.73 mg. There was no correlation between the determinations and the patient's body weight or degree of eosinophilia. His findings are in contrast to virtually all previous investigations, which reported normal cortical function in bronchial asthma.

Braun and his colleagues[38] performed pulmonary function studies before and after intravenous ACTH therapy (2 to 5 mg daily with added potassium chloride, for periods of five to ten days) on nine adult asthmatics of long standing, all of whom had emphysema. In five instances, there was improvement in all the functions investigated, including the maximum breathing capacity, the vital capacity, the breathing reserve ratio, the oxygen consumed per liter of ventilation, and the air velocity index. In the other four cases, there was no uniform change, but most of the values worsened, despite clinical improvement. It was assumed that these latter cases had less of the "obstructive" type of ventilatory insufficiency and greater loss of elasticity and other structural pulmonary changes (the "restrictive" type), or pulmonary fibrosis.

Some studies compare the relative efficacy and cost of the two hormones, and of their several modes of administration. McCombs[177] employed repeated courses of therapy in a small series of intractable cases. While incapacitating attacks were avoided and an asymptomatic state rapidly restored, the duration of remissions was short, averaging one month or less, and so retreatment was often required. Corticotropin seemed to bring about more uniformly beneficial results than cortisone, although the latter was definitely good in many instances, and ACTH in gelatine gave the best results with the smallest dosage. McCombs estimated that one unit of corticotropin is roughly equivalent in antiasthmatic activity to about 2.5 or 3 mg of cortisone. Whether or not the prolonged use of these hormones is practical or wise for the average asthmatic patient cannot be decided until more experience is accumulated. Particularly in cases with extrinsic allergic factors, they should be reserved only for the therapeutic failures. Despite their relatively high cost, they may be less expensive in the long run than hospitalization and emergency care. Intermittent therapy aided in the avoidance of the unpleasant side-effects associated with prolonged therapy. Hampton,[127] on the basis of incomplete studies, found

ACTH to be more efficacious than cortisone, and in the following relative order of effectiveness: continuous intravenous (20 to 30 mg daily for two to five days); combined intravenous and intramuscular (one daily intravenous infusion plus 10 to 12.5 mg intramuscularly at midnight); intermittent intravenous (10 to 12.5 mg once daily, requiring eight to twelve hours); and intramuscular (25 mg every six hours, reducing dosage when improvement occurs). Holler et al[138] employed "compensan," a proprietary vehicle containing a molecular complex exerting a retarding effect on the absorption of corticotropin from the blood, for the intravenous administration of ACTH. Favorable results were obtained, despite the interruption of therapy because of thrombophlebitis resulting from the use of rubber catheters. The intravenous dosage required was approximately one-quarter to one-half that required for intramuscular therapy.

Gottfarb and Sundberg[113] noted subjective relief in 90 per cent and diminution in rhonchi in 80 per cent of patients given corticotropin intramuscularly in initial doses of 40 mg four times daily and less as improvement occurred. After treatment for three days to three months, the duration of remissions ranged from a few days to a maximum of seven weeks, usually being one to three weeks. In other patients, the corticotropin was followed by oral cortisone, beginning with 50 mg daily and reducing gradually to 25 mg every other day; relapses often occurred when this final dose was reached. Like others, they concluded that the chief indication for corticotropin is severe acute status asthmaticus or chronic asthma refractory to ordinary treatment.

Segal et al[247] administered ACTH intramuscularly in eighty-two courses to fifty-two cases of intractable asthma, and intravenously in twenty-five courses to twenty cases. The results were appreciably better and the post-treatment remission tended to be longer after the intravenous therapy. They gained the impression that some of the most impressive remissions after steroid therapy were in those patients in whom disturbances of psyche were foremost. The reviewer's experience has been otherwise.

Criep[60] in discussing the fundamentals of steroid therapy, stated that it is indicated only in intractable asthma and status asthmaticus. Intravenous ACTH should be employed only in very severe cases where an immediate effect is desired, while cortisone tablets are useful for maintenance therapy. There appears to be no advantage in aerosol cortisone. Aber et al[1] found intravenous ACTH to have the best prospect of rapid relief and to be the least expensive mode of hormone therapy. Therapy was beneficial in seven of nine cases of severe asthma, but one died on the second day of therapy with mucous plugging of the air passages, which might have yielded to bronchoscopic aspiration. Cortisone aerosol (5 mg in 2 ml of normal saline at intervals of two hours) was not as dramatically beneficial as intravenous ACTH, but was judged by the patients as equally effective. In twenty-nine intractable cases treated with ACTH or cortisone by G. T. Brown,[46] there were two failures including one death. In fifteen cases of status asthmaticus reported by Hansen-Pruss,[129] three died during their second or third episode despite ACTH therapy.

It would appear that hydrocortisone (free alcohol), formerly known as Kendall's compound F, is significantly more potent than cortisone acetate, milligram for milligram, when administered orally, so that only 60 to 70 per cent as much is required to produce the same effect.[34,35,143] Because of the differences in potency, it is essential to distinguish between pure hydrocortisone (free alcohol) and the ester, hydrocortisone acetate. Bick-

erman and Barach[29] found hydrocortisone more rapidly effective, required smaller doses and produced fewer side effects than cortisone. Hydrocortisone in an average daily dose of 110 mg caused complete remission of symptoms in 75 per cent of cases and partial remission in 24 per cent; cortisone in an average daily dose of 210 mg accomplished this in 68 and 22 per cent, respectively. By contrast, ACTH was beneficial in 43 per cent of cases, the results being poorest in patients with emphysema. They concluded that hydrocortisone may be the treatment of choice. It has been suggested[143] that in chronic asthma, the integration of courses of corticosteroid therapy (administered at the first signs of recrudescence, with subsequent return to maintenance doses or withdrawal of the drug) with conventional allergy management offers the most promising approach.

In answering the problem of a patient unable to take cortisone by mouth because of uncomfortable side-effects, it was pointed out[217] that hydrocortisone may be better tolerated and also that, while corticotropin produces very much the same undesirable effects, it may in some instances be effective in small enough doses to make such reactions minimal.

Ambulatory treatment with intramuscular corticotropin was given to thirteen patients with severe asthma for a period of six days (50 mg twice daily for two days and 30 mg once a day for four days) by Andersson.[6] Subjective symptoms disappeared, usually in twenty-four to forty-eight hours, in most, but the improvement was only moderate in two cases. Subsequent remissions lasted one to sixty-seven days, but one patient developed status asthmaticus the day after treatment ended.

Repository or long-acting corticotropic hormone was employed by Levin,[162] and Bergstrand, Engström and Kraepelien.[27,28] Levin had good to excellent results in ten adults and six children with severe asthma and status asthmaticus. The adult dosage was 40 to 60 units once or twice the first day, reducing gradually to 20 units once daily for the fourth to sixth days as needed. There were no undesirable physiologic effects and no local reactions of consequence. Patients were rarely treated longer than three to five days and there was no need for "tapering-off" the dosage, because of the slow absorption. Levin believes that ACTH in gelatin will largely replace other modes of administration. Bergstrand and his associates[27,28] treated thirteen children with ordinary corticotropin and eleven with a long-acting preparation. The former was given by injection four times a day, and remissions lasted from less than a day to fifteen weeks; the latter was given once every second or third day, and in some cases every fifth to seventh day, and the duration of remissions was also variable, the longest being three months. If a rapid effect is desired in attacks endangering life, regular corticotropin is preferred, but the long-acting corticotropin makes ambulant treatment possible and requires a smaller daily dose.

Attempts at prolonged hormone therapy continue. Howes[141] reported in detail on six cases with severe incapacitating asthma given oral cortisone maintenance therapy for five to twenty-one months. Average daily maintenance dosage requirements varied from 20 to 75 mg in four divided doses. In two cases the results were unsatisfactory from the long term point of view. It appears likely that therapy will have to be continued indefinitely in the others. Intercurrent infections require prompt antibiotic therapy and a temporary increase in the dosage of cortisone. It is concluded that the method is suitable for only a few highly selected cases and should be used only when absolutely necessary. Burrage and Irwin[50] would limit cortisone therapy to cases of status asthmaticus not responding

to the usual emergency treatment; to seriously ill patients who despite hyposensitization have developed severe pollen asthma that resists routine therapy; and to a small group with constant intractable perennial asthma in whom the etiologic diagnosis has not been established despite extensive study and in whom negligible relief follows all types of routine therapy. In the last group, maintenance cortisone therapy over many months proved useful. However, treatment was not always effective, one patient dying despite both cortisone and ACTH. Dosage problems arose, since symptoms often recurred at the lower dosage levels. No patient remained symptom-free on less than 25 mg of cortisone per day. Once the optimum daily dose was established for a patient, it did not seem to fluctuate materially. Gelfand[106] reported eighteen cases given cortisone or ACTH or both for periods from a few weeks to two years. Excellent results were obtained in all but three cases. The optimum program appeared to be one starting with oral cortisone, 200 mg daily, stepped down to a maintenance dose as improvement started, and accompanied by ACTH gel, 10 to 20 units intramuscularly once or twice a week. Clinical symptoms recurred sooner or later after the hormones were withdrawn, unless the irritating factor was eliminated. Swern and Cagan[270] successfully treated a patient at home with intravenous ACTH administered when required every few days, in two courses lasting one and two months.

Long-range therapy with cortisone or hydrocortisone was employed by Arbesman and Richard.[9] The initial dose of the former was 300 mg the first day, tapered off to an average of 50 to 75 mg daily, and of the latter 240 mg with a maintenance dose between 40 and 60 mg daily. Of sixty-three cases of chronic asthma, the results were excellent in two, good in thirty-nine, fair in fifteen, and poor in seven. In three aspirin-sensitive patients, the asthma was aggravated by cortisone and hydrocortisone. The authors recommended that ACTH therapy be interpolated in the cortisone or hydrocortisone regimen every few months. According to Baldwin et al,[15] prolonged continuous or intermittent treatment with ACTH or cortisone was effective in 87 per cent of sixty patients. While such therapy did not seem to lower resistance to intercurrent infections, their prompt recognition and appropriate therapy is of the utmost importance.

Steroid therapy is effective in pollen asthma, according to Schiller[241] and Roy[231] and their colleagues. The former employed 100 mg of cortisone acetate per day in four divided doses, given for just four days. Six cases had complete relief of both pollen asthma and hay fever, one had a satisfactory response, and three failed to benefit. Most patients had had previous pollen injections. Relief usually appeared on the second day of treatment. Relapses occurred after two to six days in three cases. Repeated courses usually gave similar results. In no instance was the asthma benefited while the hay fever persisted or *vice versa*. Roy et al[231] gave daily intramuscular injections of 40 units of ACTH gel for from two to nineteen days in eight cases of ragweed pollen asthma and hay fever. While generally benefited, these cases appeared to be slightly more resistant to hormonal therapy and showed a greater incidence of recurrences than those patients with hay fever only. An editorial[83] gives qualified approval to the hormonal therapy of seasonal allergies, but only for symptomatic management of those patients failing to respond to more conservative measures. The choice of corticotropin or adrenal corticosteroids depends on an "inspired guess whether a hypofunction of the pituitary or of the adrenal cortex is the lesser of two evils, and on the convenience of administration."

A suggested schedule is 80, 60, 40, and 20 units of corticotropin, each dose repeated on two consecutive days. Even this transitory treatment requires careful supervision.

The untoward effects of the hormonal treatment of asthma must not be forgotten. Wofford[293] lists the complications of therapy as (1) increased severity of symptoms after cessation of treatment, usually occurring in one or two weeks; (2) psychic insult on the return of symptoms; (3) development of sensitivity to ACTH or cortisone—more likely, in the form of urticaria, with the former, although cortisone can induce asthma; (4) full-blown development of masked secondary infections, such as pneumonia or appendicitis, as well as peptic ulcer; (5) Cushing's syndrome; (6) miscellaneous side effects; and (7) death. Urticarial reactions were reported from cortisone and ACTH by Sèze et al[250] and Löffler's syndrome from ACTH by Holler,[137] although their patients were not being treated for asthma. Of 600 patients treated with ACTH for a variety of conditions, Shulman and his colleagues[252] observed five cases of the serum-sickness-type allergic reaction; in two cases each the sensitivity was to beef ACTH and porcine ACTH, and in the other to the hormone derived from either source. Chronic hallucinosis followed ten days of cortisone therapy in an asthmatic treated by Léchelle et al, [156,157] and osteoporosis appeared in some of the asthmatic patients treated with cortisone by Irwin et al.[144]

Two fatalities reported by Järvinen[146] during cortisone therapy of asthma revealed necropsy evidence of acute peripheral circulatory insufficiency, as well as cor pulmonale, pulmonary emphysema, acute congestion of the gastrointestinal tract, and, in one case, obstructing mucus plugs in the bronchi. Despite the absence of definitive evidence, the possibility that cortisone played a part in the fatal outcome could not be excluded. In a thirteen-year period, 617 asthmatics were admitted to one hospital and ten died, though asthma was the immediate cause of death in only four. Since only twelve patients received cortisone and two died, the disproportion is striking. At a clinical pathological conference[54] at New York University—Bellevue Medical Center, the possibility that ACTH contributed to the demise of a patient with status asthmaticus was considered.

Lewis and his coworkers[164] reported a fatal adrenal cortical insufficiency precipitated by a relatively routine orthopedic surgical procedure during prolonged continuous cortisone therapy of a patient with rheumatoid arthritis. Death was attributed to the stress of general anesthesia and surgery superimposed upon the cortisone-induced adrenal insufficiency. The frequent occasion for surgical intervention in asthmatics under treatment with adrenal or pituitary hormones emphasizes the necessity for adequate preparation and hormonal support of such patients during periods of stress. Lewis' detailed instructions for the preoperative and postoperative management of this situation should be familiar to everyone facing this problem.

It is stated that a natural steroid complex known as Marisone and derived from pregnant mare's urine from which the estrogen conjugates have been removed, has some of the physiologic actions of cortisone. Millman and Maggio[187] gave seven patients with intractable asthma 1 to 2 gms of this material daily for periods of six weeks to seven months. Five patients showed moderate or marked improvement, and all of these were emotionally unstable and under tension. Subsequent exposure to known allergens generally resulted in less severe and less prolonged attacks than usual. The only major side-effect was tenderness and swelling of

the breasts and nipples after several weeks of therapy. Bloom and Markow[32] employed 600 to 1200 mg daily in divided doses. The results were considered excellent in seven, good in eight, and poor in sixteen cases. However, the improvement did not persist in most instances despite continued medication, and there appeared to be no protection against recurrent attacks or exacerbations of the asthma. Side reactions occurred in 27 per cent of the patients treated.

TREATMENT: IRRADIATION

According to Poulsen,[202] roentgen therapy resulted in reduction in the severity or complete cessation of asthma in forty of forty-eight patients treated. Relief usually began about one week after the end of treatment, and lasted for two months or longer. Therapy involved two anterior and two posterior fields directed to the hilar area with 0.5 mm Cu plus 1.0 mm Al filtration at 30 cm distance at 160 kv to a total of 100 r to each field. Two fields were irradiated at a time and treatment required a total of eighteen days. There were no untoward effects. Roentgen therapy was recommended as a palliative in middle-aged and elderly patients with long-standing disease, and should not be used in children. It should not be given until all other therapy has been given a trial. This in agreement with the opinion[216] that X-ray treatment for asthma is not justified as the first therapeutic approach, and particularly not in children. When allergic and usual methods have failed, it may be helpful in some cases.

The relationship of endogenous asthma to the central nervous system was the basis of the studies performed by Jacquelin and his colleagues.[145] In some patients asthma is related to a constitutional derangement of the diencephalothalamic region, and in others to fear of attacks or to sudden emotional shocks. In line with this concept, it was found that a single intramuscular injection of 2 gms of a completely deproteinized diencephalic extract caused vasomotor disturbances and attacks of asthma, while daily injections of 0.5 to 1.0 gm of the extract for twenty days produced remissions lasting weeks or months in four of seven cases. Accordingly, twenty-eight patients were given roentgen irradiation to the diencephalon with 50 r once a week for fourteen weeks. While asthma followed one of the initial three exposures in some instances, eleven patients had complete remissions after the third to fifth treatment, six were considerably improved, three were temporarily helped, two were failures, and treatment was discontinued in six. Transitory polyuria, vasomotor phenomena, headache, somnolence or insomnia occurred occasionally. The patients who were benefited by irradiation had frankly paroxysmal asthma and eosinophilia.

Van Went[285] applied ultra-short wave therapy to the pituitary to induce endogenous ACTH formation and release; seven minutes with the ultratherm apparatus was given twice a week. Blood eosinophils were found to drop in one-half to one hour in almost all instances. Van Went claimed no treatment failures in fifteen cases.

TREATMENT: SURGERY

Sobel[258] observed the results of adenotonsillectomy in patients with asthma of predominantly infectious type. The relationship of the tonsils and adenoids to bacterial asthma is still in dispute, and the three major schools of thought are summarized by her: (1) Adenotonsillectomy will be beneficial, since the tonsils and adenoids can act as foci of infection; their early removal in a potentially asthmatic patient can prevent asthma. (2)

Adenotonsillectomy may make the asthma worse, since infection can spread more easily from the upper respiratory passages; the operation may precipitate asthma or convert mild asthma to severe asthma. (3) Adenotonsillectomy will not affect the course of asthma and the indications for the operation are the same in allergic and nonallergic patients. Of twenty-eight patients who had asthma before the operation and before coming under allergic management, 82 per cent had recurrence of the asthma within one year, and all of them within four years of the operation. Of forty patients who developed asthma for the first time after adenotonsillectomy, 28 per cent did so within one year, and 40 per cent within two years. It is strongly suspected that most of the "recurrent colds" which constituted the chief indication for the operation were in reality allergic rhinitis. There were no differences in the degree of severity of the asthma between the patients with intact tonsils and adenoids, and those who had them removed. Only four patients required tonsillectomy and adenoidectomy after allergic treatment was instituted, showing that many of the indications for this operation may no longer exist after proper allergic therapy. Four cases were observed to have an immediate onset of severe asthma after operation during the ragweed season. It is concluded that the indications for the operation are the same in allergic and nonallergic patients, and that adenotonsillectomy does not affect the severity of asthma. A recent symposium[272] on the tonsil and adenoid question does nothing to clarify the problem.

Patrick and Lundy[198] considered the problems of anesthesia in the asthmatic patient. Morphine, parasympathomimetic drugs such as Pentothal Sodium and Cyclopropane, and agents known to release histamine, such as curare, are to be avoided. Aspiration of stomach contents into the tracheobronchial tree under anesthesia may cause an expiratory wheeze which must be distinguished from the characteristic wheeze of asthma. An asthmatic attack in the course of anesthesia should be treated with high concentrations of oxygen and with bronchodilators. Switching to ether will frequently prevent recurrence of asthma during the maintenance of anesthesia.

TREATMENT: ANTIBIOTICS AND VACCINES

Numerous reports favor antibiotic therapy for the control of superimposed infection in the asthmatic patient or for infectious asthma. Shuey and Grater[251] point out that the differentiation is not always possible and that cultures do not invariably give consistent results. Most of their twenty-five patients received considerable benefit therapeutically and prophylactically from procaine-penicillin, streptomycin and dihydrostreptomycin or gantrisin, separately or in combination, continued for one to six months. According to Finke,[96] prolonged antibiotic therapy rehabilitated many advanced cases and cured early cases of infectious asthma in 244 patients treated or followed for an average of nearly three years. Although penicillin was used principally (by injection, mouth or aerosol), concomitant administration of other antibiotics proved beneficial in some cases. These included terramycin, chloramphenicol, aureomycin, and parenteral and oral streptomycin and dihydrostreptomycin. Antibiotic sensitivity tests proved misleading. Absenteeism in treated patients was about one-half that in controls. General health and pulmonary function were much improved in children. Acquired resistance did not constitute a clinical problem.

The effectiveness of antibiotics in bronchial asthma in allergic individuals —even in the absence of obvious infection—is striking, according to Miller.[183] He stated that refractory cases deserve antibiotic trial even when

evidence of infection is lacking. Derbes[71] pointed out that upper respiratory infection may prolong status asthmaticus by narrowing the bronchial air space by purulent exudate. By removal of the infectious element, the asthma may be made to subside even though the basic allergic state is unaffected. Broad-spectrum antibiotics may be given arbitrarily, or the sputum may be cultured and antibiotic sensitivity tests performed. In any case, if the sputum is purulent, antibiotic therapy is clearly indicated.

Langley[155] holds that the terms asthmatic bronchitis, bacterial asthma, infectious asthma and intrinsic asthma are really synonymous, since the relation of bacterial allergy to asthma is not clearly understood. He administered 500 mg of chloramphenicol every six hours to thirty patients, for a total of 6 to 15 grams of the drug. There was definite benefit in the majority of cases, although the relief was not enduring. Many difficult cases were helped, though least so in those with irreversible emphysema. Relapses occurred in all cases within three to six months, each time after an acute upper respiratory infection. Repeated courses were sometimes beneficial. The best results were obtained in those cases in which *Streptococcus mitis* was the predominating organism in the sputum.

Dulfano and Segal[78] had favorable results from penethamate hydriodide (neo-penil), one-half to one million units daily for five to twelve days, in ten patients with chronic bronchial asthma and pulmonary infection. Sputum penicillin levels were found to be consistently higher than in the blood. Simon,[254] on the other hand, in an equal number of cases of intrinsic asthma given neo-penil (500,000 units every twelve hours) for fifteen days, followed by terramycin for seven days, felt that the results were not striking and that chronic infections were little if at all affected. The vital capacities increased only about 10 per cent and this could have resulted from rest alone. He also found that antibiotic aerosols, including streptomycin, neomycin, polymyxin, terramycin, bacitracin, and aureomycin, gave inconclusive results. Certainly, most clinicians favor appropriate antibiotic therapy in selected cases and many employ aerosols.

Barach et al.[23] administered aureomycin, terramycin or chloramphenicol to forty-five patients with chronic bronchitis associated with bronchial asthma or pulmonary emphysema. Marked or moderate benefit ensued in thirty-seven of them. In such cases, extension of the pulmonary disease and increased bronchospasm may follow an acute exacerbation of the chronic disease process. Treatment with the broad-spectrum antibiotics for five or six days has the advantage, in most cases, of prompt control of the infection with a minimum of allergic response. Preliminary results with neo-penil indicated an especially favorable response in infections due to Gram-positive bacteria. In the elderly asthmatic, Barach[17] recommended antibiotic and physiologically directed therapy. In this group, with pulmonary emphysema, acute upper respiratory infections are often difficult to diagnose, and pneumonitis often ensues. Penicillin and a broad-spectrum antibiotic should be administered simultaneously for the first five days. In certain undifferentiated infections, therapy may be deferred, but if the expectoration becomes purulent or if pyogenic organisms are cultured, oral penicillin, streptomycin or a broad-spectrum antibiotic may be given according to the organism.

The risks of antibiotic therapy should not be overlooked. According to an editorial,[79] for persons with an allergic diathesis, an antibiotic should be among the last rather than the first remedies chosen. Among the fourteen cases of fatal anaphylactic reactions to penicillin accumulated by Collins-Williams and Vincent,[59] four occurred in patients with asthma.

Curphey[65] reported the autopsy findings in two asthmatic patients who both died within a few minutes of intramuscular injections of penicillin. In one case, there was marked hyperventilation of all lobes of the lungs, but a paucity of microscopic changes. In the other, marked eosinophilic infiltrations were found in the lungs, spleen and bone marrow. In another case discussed at a clinical pathological conference,[39] it was thought possible that penicillin contributed to the demise.

Sterling[264,265] observed nine instances of anaphylactic shock following the injection of penicillin in asthmatics, and three were "almost fatal." While skin testing with penicillin was found to be unreliable, the occurrence of symptoms following previous injections will constitute a warning. Asthmatic manifestations may result from penicillin sensitivity, according to Shulman et al.[252] Reichlin and his colleagues[228] described a case of Löffler's syndrome following penicillin therapy, in a patient with a history of hay fever.

Autogenous vaccines have been disappointing to Simon.[254] He favors a nonspecific bacterial filtrate prepared from stock cultures obtained from bronchoscopic specimens from asthmatic patients and subjected to a ball mill for forty-eight hours before Seitz filtration. Skin tests gave many immediate whealing and delayed reactions, but had no prognostic value. Some patients had asthmatic attacks several hours after the injection of the larger doses, but no other constitutional reactions.

TREATMENT: PYROGENIC AGENTS

Opinions differ regarding the value of injections of Piromen,® a *Pseudomonas* polysaccharide in colloidal dispersion. Aronoff and Ghaemi[10] administered it subcutaneously, except in severe cases, and changed to intravenous injection if improvement did not occur. Injections were given every two to four days, in increasing dosage from 1 or 2 gamma until a constitutional reaction was obtained or a dose of 10 gamma was reached. Results were considered good in twelve cases, fair in two, and poor in five. A pyrexial response was not necessary for a favorable effect. Fenton[95] employed Piromen as an adjunct to other therapy, in courses of ten to fifteen injections and repeat courses of eight to ten injections. No patient received more than four courses. Dosage was individualized, beginning with 0.5 to 1 gamma. Results were excellent in four cases, fair in three and poor in six.

MacLaren and Frank[173] gave Piromen to thirty-nine cases. Only three were consistently better, and six relapsed while still receiving injections. About 90 per cent had no real relief. They concluded that Piromen in subfebrile doses has no specific effect on allergic disease. Fond[98] followed the course of twenty-six cases with weekly physical examinations, maximum breathing capacity and vital capacity determinations. No significant changes occurred during or for eight weeks after Piromen therapy. Simon[254] likewise observed no evidence of objective benefit in thirty-two cases of intrinsic asthma. All authors refer to frequent side effects of the therapy.

TREATMENT: PHARMACOTHERAPY

Halpern[125] reviewed the pharmacology of the drugs employed in the symptomatic therapy of asthma, including those acting on the autonomic nervous system, antispasmodics, and antihistaminics. It is pointed out that when their physiologic properties and their therapeutic effect on human

asthma are compared, a number of paradoxes appear. For example, atropine is ten times more effective than epinephrine in combating experimental smooth muscle spasm; papaverine is 300 times more potent than aminophylline in intestinal spasm in rabbits and two to four times more than theophylline in acetylcholine- or histamine-induced bronchial spasm in guinea pigs. Yet both drugs are ineffective in asthma. Antihistaminics control the oculonasal symptoms of pollinosis but are not efficacious in pollen asthma. The true mechanism of the therapeutic action of the drugs commonly employed in asthma is most complex and only partially understood.

Mixtures of bronchodilator drugs have long been useful in therapy. Bickerman and his coworkers[30] compared the clinical effectiveness of three commercial preparations in patients with asthma and pulmonary emphysema. Moderate to excellent relief of bronchospasm occurred in 52 per cent of patients taking Nephenalin® (N-isopropylarterenol hydrochloride, theophylline, ephedrine sulfate and phenobarbital); 72 per cent with Dainite (ephedrine hydrochloride, aminophylline, aluminum hydroxide, ethyl aminobenzoate, sodium pentobarbital); and 75 per cent with Cardalin (aminophylline, aluminum hydroxide and ethyl aminobenzoate). Ventilatory function studies showed a mean rise of approximately 10 per cent in vital capacity and 10 to 20 per cent in the maximum breathing capacity following administration of each of these preparations. They failed to relieve severe intractable asthma. The incidence of side effects was small.

Nephenalin Pediatric, containing N-isopropylarterenol hydrochloride in the outer coating and ephedrine sulfate, theophylline and phenobarbital in the inner portion, was given a clinical trial in fifty children with moderately severe to severe asthma by Dees et al.[70] Effective relief was obtained in approximately 66 per cent of cases, and there were only few unpleasant side effects. The preparation was administered as necessary and the trials extended for three weeks to one year. Relief occurred in two to thirty minutes when it was effective.

Antihistaminic Drugs.—The attitude of most allergists toward the antihistaminics is well expressed by Haag.[122] "In spite of the fact that it has been demonstrated that these drugs are generally of little or no value in the treatment of asthma, their use for this purpose still seems to be rather widespread."

There is a fairly general belief that hay fever patients given antihistaminics as the only treatment are more likely to develop asthma than those who receive no therapy. Frankland and Gorrill[102] were unable to confirm this. They conducted a "blind" comparison of a new antihistaminic with mepyramine maleate (also known as anthisan, pyranisamine maleate and neoantergan) and with an inert tablet in a number of cases of summer hay fever and asthma. The antihistaminics did not increase the incidence of asthma, nor did they relieve it when it was present. The hay fever symptoms were less likely to respond to antihistaminic therapy if the patient also had asthma. Swartz[269] confirmed the last observation as regards diphenylpyraline, a new antihistaminic. Though effective for uncomplicated hay fever, it did not benefit associated asthma.

Spearman[261] found that, although the inclusion of 3 to 15 mg of Chlortrimeton® in the syringe containing hyposensitizing allergens was a useful technique in treating hay fever and perennial rhinitis, it gave poor results with bronchial asthma.

A committee headed by Arbesman[8] reported that Copyronil® was relatively more effective in asthma than Pyronil.® The difference is presumably due to the clopane hydrochloride contained in Copyronil. Baird[14] found that intramuscular injections of 50 mg of Phenergan was valuable in the majority of asthmatics, especially those overstimulated by epinephrine. Injections were given two or three times a day, and some patients were placed on oral dosage after a few days. The treatment was ineffective in a few cases with a considerable degree of bronchitis. Intramuscular Phenergan appeared not to be toxic or habit-forming; one patient received 600 ampules in five and one-half years.

Schaffer[239] observed personality changes in nineteen asthmatic children induced by one of four antihistaminics. The alterations consisted principally of irritability, antagonism or weepiness.

Mothersill et al[191] reported that pyrrobutamine (Pyronil) has a relatively greater and more prolonged effect in guinea pigs against asthma induced by histamine aerosol than any of five other antihistamines. Naranjo and Banda de Naranjo[193] showed that certain combinations of antihistaminics are much more potent in this respect than their individual constituents.

Procaine.—Criep and Castilho Ribeiro[64] reported three fatal immediate reactions to procaine hydrochloride used for local anesthesia. One patient was a known asthmatic, who developed marked bronchospasm and died shortly after routine preparation for bronchography with 1 per cent procaine hydrochloride. Davis and Bryce-Smith[68] refused to accept the explanation of the allergic nature of the reaction and attributed the bronchospasm to a foreign body (iodized oil) in the trachea.

DeBold and Fox[69] observed three reactions from 1,600 intravenous injections in 300 patients, mostly nonallergic. Of the reactions, one occurred in an asthmatic and one was characterized by asthma-like symptoms.

Khellin.—Visammin and its derivative, khellin, have been used by various modes of administration. Kennedy and Stock,[153] while emphasizing the difficulties of objectively assaying bronchodilator action, found the expiratory flow rate was significantly improved after daily oral doses of from 50 to 400 mg or intramuscular doses of 150 to 400 mg in three cases of chronic asthma. In two other cases, and in several cases of chronic bronchitis with emphysema, the findings were inconclusive. The action of khellin was slow to appear, but single doses had sustained action over a period of one or two days, and repeated doses had a cumulative effect. Side effects, mainly nausea, were frequent, but less common after injection than after oral administration. Epinephrine aerosol was found to have an additive effect when given at the same time. Visammin was given orally and rectally to nineteen patients by Merli and Mariani[182] in daily doses of 100 to 200 mg, later reduced gradually to 50 mg. The results were satisfactory in most patients. Asthmatic attacks were relieved in a few minutes and subsequently were less frequent and less severe. The effects of the drug appeared to be proportional to the dose given. Mulligan[192] employed oral doses of 40 mg of khellin twice or three times a day for at least six months in a group of patients with chronic nonseasonal asthma. Twenty-two cases had good or excellent results, and four each had fair and poor results. About one-half had some nausea, but only one patient had to discontinue the drug; one other reported a debilitating languor. Suppositories of khellin were effective in two patients.

Intravenous khellin (in a vehicle containing sodium salicylate) was used by Brügel and Henne.[47] Dosage was usually 20 mg twice daily, but in some instances 40 mg. The results were good in four cases, fair in seven, doubtful in three, and unsatisfactory in eight. Three patients suffered a sudden drop in blood pressure. The preparation is deemed more useful in acute attacks and in status asthmaticus rather than for prolonged treatment.

H. S. Tuft[275] provided a preliminary report on a new intramuscular preparation, a suspension of crystalline khellin in isotonic saline solution. Previous preparations employed a number of different vehicles. Doses of 50 or 100 mg were given intramuscularly once or twice a week. Twenty-eight patients had moderate improvement, four had slight improvement, and five remained unimproved. The patients with perennial, chronic symptoms and daily wheezing seemed to be most benefited. The relief usually started some hours after an injection and persisted for three to five days. Asthma returned when the injections were discontinued. Local reactions were slight and infrequent.

Adrenergic Agents.—An interesting historic footnote was presented by Haughey[133] who described what is claimed to be the first time epinephrine was administered for asthma in August, 1906. The patient was his mother, who had seasonal asthma, and the first dose was 20 minims of a 1:1,000 dilution! As might be expected, the side effects were impressive, but subsequent smaller doses were helpful.

The use of epinephrine in asthmatics with hypertension, coronary insufficiency or arteriosclerotic heart disease was recently discussed.[215] While caution is enjoined in the presence of cardiovascular disease, because of the pressor and cardiac excitatory actions, the need must be weighed against the possible harm. Since an asthmatic attack usually elevates the blood pressure, relief of dyspnea with epinephrine may actually lead to a decreased pressure in the hypertensive patient. Aminophylline is, of course, more desirable. If epinephrine produces severe tachycardia, it is contraindicated in arteriosclerotic heart disease and in coronary disease. There is evidence, however, that it dilates the coronary vessels.

The clinical usefulness of Sus-Phrine (a 1:200 suspension of epinephrine in an aqueous vehicle) was confirmed by a committee headed by Arbesman.[8] In doses of 0.1 to 0.3 cc subcutaneously, it was well tolerated except for slight local stinging and was effective up to twelve hours, but generally not as long as epinephrine in oil. It may produce the usual side effects of epinephrine and in some instances these are rather prolonged.

The addition of 100 mg of benzyl nicotinamide to sublingual tablets of isopropylarterenol was found by E. Brown[41] to increase its therapeutic effectiveness and modify its action on the heart.

Leslie, Blahd and Adams[161] studied the effects of prolonged administration of epinephrine (injections one or more times a day for months or years) on adrenal cortical activity in five patients with chronic asthma. The hypothalamus-pituitary-adrenal cortex mechanism did not appear to be in a state of chronic stimulation. Adrenal cortical function, as indicated by the effect of ACTH on the level of circulating eosinophils and on the sodium concentration of sweat, was in general unimpaired. Temporary discontinuance of epinephrine did not lead to an appreciably enhanced anti-asthmatic effect when the drug was restored. There was no reason to believe that adrenal cortical function was impaired in intrinsic asthma. Epinephrine was found to have only a brief effect on the pituitary-adrenal mechanism

which rapidly became refractory to further epinephrine. Nevertheless, epinephrine continued to relieve asthmatic manifestations for variable periods of time, and therefore was deemed to act directly as a bronchodilator.

McDougal and West[178] compared the effectiveness of various adrenergic drugs in preventing histamine- or acetylcholine-induced spasm of isolated human bronchial rings and animal tracheal rings. There was considerable variation in the responses of the human material, and also between the various animal species. Noradrenaline was about 100 times less effective than synthetic *l*-epinephrine in the human material. Isoprenaline (*d-l*-isopropylnoradrenaline hydrochloride) was the most active bronchodilator. Ephedrine had only weak dilator properties, but unlike aminophylline which was more effective against histamine than acetylcholine bronchospasm, was equally effective against both types. Combined experiments suggested that the ultimate site of action of sympathomimetic amines is different from that of aminophylline.

Parasympathetic Blocking Agents. Dann et al.[66] compared the effectiveness of Prantal® methylsulfate, a synthetic anticholinergic compound, with other drugs by means of vital capacity and maximum breathing capacity determinations on twenty-four patients with asthma. Intramuscular injections of 25 mg of Prantal proved to be equal in effect to 500 mg of aminophylline intravenously or 0.25 mg of epinephrine intramuscularly, and inferior to 0.5 mg of epinephrine, but superior to 50 mg of ephedrine intramuscularly. The majority of patients testified to satisfactory subjective relief. There were a number of side reactions of atropine-like type, chiefly dryness of the mouth and throat, less often mild dizziness, "pins and needles" sensations, headache and blurring of vision. No significant mydriasis was noted. The toxicity was mild and not a deterrent to the use of the drug. Oral doses of 50 mg were ineffective and addition of Chlortrimeton® did not yield impressive results. Other anticholinergic substances should be investigated in the hope of finding one with a more specific effect on the bronchus and with a minimum of unpleasant side effects.

Other Preparations.—Gregory et al[116] tried intravenous tetraethyl ammonium chloride (Etamon or TEA), a ganglionic blocking agent, in twenty asthmatics. In doses of 7 mg per kg, relief of asthma occurred more frequently than aggravation. In some cases, epinephrine in doses of 0.2 to 0.6 mg intramuscularly following the TEA relieved a previously refractory status asthmaticus, but in other cases failed to do so. Whether sensitization to or increased secretion of endogenous epinephrine and/or norepinephrine occurs following administration of TEA could not be determined. A significant increase in vital capacity followed intravenous TEA in sixteen instances, a decrease six times, and no change thirteen times. By contrast, epinephrine almost invariably caused an increase. However, in five cases refractory to epinephrine, three had relief from TEA, while in two cases refractory to aminophylline there was no effect of TEA. The drug relieved histamine-induced asthma in two of three trials. One severe case of status asthmaticus in coma and *in extremis*, previously refractory to epinephrine, aminophylline and oxygen, responded dramatically to 0.2 cc of TEA intravenously. In preliminary trials, Banthine, both a ganglionic blocking and anticholinergic agent, was found to have a favorable influence on vital capacity in some cases.

Quinoline compounds, derivatives of quinine, have been used as antimalarial drugs. Aureoquin (6-methoxy-4-amino quinoline) has anticholinergic, antihistaminic and probably bronchodilator properties, according to Geschickter.[107] Administered to 155 children, fifty young adults, and eighty adults over forty years of age, all with asthma, it produced benefit in nearly all, treatment failures constituting 2.5, 5 and 10 per cent, respectively. There were complete remissions in 25 per cent of the cases followed for two to four years after treatment was discontinued.

Phenarsenide, a flavored liquid containing arsenious iodide in amounts equivalent to 18 mg of arsenious oxide per fluid ounce, was employed by Fishman[97] in forty-five cases of chronic asthma. Doses averaged 2.5 to 5.0 ml three or four times daily, but were individualized. Thirty-three cases had effective relief, six had none, and six had to discontinue treatment because of iodiosyncrasies, including rash, rhinitis and headache. The drug is contraindicated in cirrhosis of the liver, chronic nephritis, and patients sensitive to iodides and arsenic.

Two reports attest to the dangers of potassium arsenite (Fowler's solution) in the treatment of asthma. The patient observed by Prickman and Millikan[203] developed hemorrhagic encephalopathy after taking such a preparation for about one month. The course was stormy and prolonged, and the authors feel that the prompt administration of dimercaprol (BAL®) may well have saved the patient's life. Harris[131] reported two cases of arsenical dermatitis in children due to an "asthma remedy" containing Fowler's solution. Dimercaprol was used successfully in one.

Potassium iodide is still the best expectorant in asthma,[209] although hydriodic acid may be used in children. Other expectorants that may be useful in asthma or croup are those that are emetic in large doses, such as ipecac or apomorphine. The stimulating expectorants, such as ammonium chloride or terpin hydrate, are helpful when the sputum is not thick, as in ordinary bronchial infection. Hagenbach and Walmsley[123] found that intravenous colloidal iodine (Crookes Laboratories' "iodine B.P. in protein combination" containing 0.8 per cent of iodine) every day or two in amounts of 20 to 40 ml given slowly, in courses of nine to twenty-six injections, brought relief for three to twelve months in most of eight asthmatics so treated.

On the basis of the theory that allergic diseases result from "histamine-epinephrine imbalance" and that a better balance can be achieved by keeping the body "saturated" with epinephrine precursors, Spickard[262] employed a mixture known as Tyral (or with the tyrosine content doubled, as T.P.N.). Tyral contains 200 mg of *l*-tyrosine, a presumed epinephrine precursor, 2.5 mg of pyridoxine hydrochloride, which in phosphorylated form is a necessary coenzyme in the conversion of tyrosine, and 10 mg of niacinamide, which also aids in the conversion and is thought to have antihistaminic properties. Of forty-three pediatric asthmatic patients, thirty-three improved on treatment. MacLaren et al[174] compared the effects of this combination with a placebo of identical appearance and observed no significant differences in twenty-seven cases, nor any benefit in eight other cases. Side reactions appeared in 18 per cent of the group.

Tausig et al[273] compared the results of the inhalation of ether with those obtained with rectal administration in status asthmaticus over a period of eleven years. Good to excellent results were obtained in 52 per cent of eighty-eight treatments with inhalation and in 24 per cent of forty-four rectal administrations. In most cases, wheezing and decreased tidal volume persisted until the anesthesia was deep in plane 3 of stage III, when

bronchodilatation seemed to occur. The level was maintained for thirty to forty-five minutes. Bronchial secretions may be suctioned off via an orotracheal catheter or by bronchoscopic drainage. Premedication included atropine or scopolamine and sometimes cautious sedation. In some cases, asthmatic breathing recurred as soon as the anesthesia lightened. Rectal ether apparently did not achieve the same depth of anesthesia as regularly. Less seriously ill cases were given 5 to 10 per cent of alcohol intravenously, with good results in 51 per cent of fifty-nine trials.

Howell[140] found that aerosol of a 10 per cent solution of calcium chloride was effective in relieving the wheezing of acute and chronic bronchitis. When indicated, penicillin can be dissolved in the same solution.

TREATMENT: OTHER ASPECTS

Aerosol trypsin was employed by Unger[282,283] and Prince,[204] parenteral trypsin by Innerfield,[142] and aerosol pancreatic dornase by Salomon[236] and their colleagues. Trypsin derived from mammalian pancreas is administered by aerosol technique to loosen or dissolve the thick tenacious materials which interfere with the breathing of patients with asthma or other respiratory conditions. Pretreatment consists of injections of epinephrine and an antihistamine. Unger and Unger[283] then give 75,000 units dissolved in 1.5 cc of Sorensen's phosphate buffer solution. If no reactions occur, the dosage is increased by stages to 125,000 units in 2.5 cc. A treatment takes ten or fifteen minutes, employing a glass or plastic nebulizer and a BLB mask rebreathing apparatus. Eight cases of paroxysmal asthma given one to eight treatments gave excellent results in four and good in two. Patients with chronic asthma and emphysema who most sorely need relief gave the poorest results: excellent in five, good in ten, and no apparent relief in eighteen. It is possible that in these cases the enzyme did not descend far enough down the bronchial tree. Favorable results were obtained in a large majority of cases of asthma complicated by infectious bronchitis or pneumonitis, and of cases with bronchiectasis some of whom had asthma. Untoward reactions consisted chiefly of transitory hoarseness in seventeen instances and increased asthma five times. Generally speaking, the thicker and more copious the sputum was, the better the results were. Prince et al[204] gave one to ten similar treatments in amounts of 62,500 to 250,000 units to nine cases of atopic asthma with secondary infection and to eight cases of chronic asthmatic bronchitis (primarily infectious asthma). The evaluation of the results was difficult because of concomitant antibiotic, symptomatic, expectorant, and allergic therapy. Their general impression of the use of aerosol trypsin to increase expectoration in the asthmatic patient with either primary or secondary bronchitis was one of disappointment. Only two patients obtained clear-cut benefit and five had questionable benefit. Asthma was aggravated in one patient and laryngeal irritation occurred in another. Trypsin aerosol can cause bronchospasm in some cases, according to Barach.[17]

Desoxyribonuclease derived from beef pancreas and known as pancreatic dornase, like the similar enzyme of streptococcal origin (streptodornase), is capable of degrading or depolymerizing desoxyribonucleoprotein which is a constitutent of purulent exudates and determines its character and viscosity. Dornase has less action on fibrin and mucus. Salomon et al[236] gave aerosols of pancreatic dornase to patients with various pulmonary disorders, including five with chronic asthma, of whom three were in status asthmaticus. The results were less striking in the asthmatics,

but seemed better when the aerosol was administered with intermittent positive pressure breathing rather than with constant oxygen flow. There were no side effects and no hoarseness, but sensitization is deemed possible. The amount of obstructing secretions may account for the variability in results, but the method seems to be of value in the evacuation of viscous, tenacious mucopurulent secretions.

Although they were primarily dealing with other conditions, Innerfield and his coworkers[142] included seventeen cases of asthma in their series treated with intravenous trypsin. An average dose of 10 mg along with 10 mg of methapyrilene hydrochloride (Histadyl®) was given for an average of fifteen treatments. They noted an amelioration of symptoms and thinning of the mucus. Parenteral trypsin, in a manner as yet unexplained, tends to accelerate the subsidence of inflammatory processes by activating a system of naturally occurring enzymes.

Ravenel[226] observed a sputum-liquefying effect of the aerosol of Alevaire which contains glycerine, sodium bicarbonate, and an alkylaryl polyether alcohol as a wetting agent, in distilled water. The infant is placed in the prone 15 degree Trendelenburg position in a plastic tent or "croupette." The results in forty cases of severe asthma and allergic bronchopneumonia, and in twenty cases of capillary bronchitis, or bronchiolitis, were considered excellent. The usual ancillary measures, including hydration, bronchodilating drugs, antibiotics, iodides, and, if necessary, corticotropin, were employed. Barach[17] reported that Alevaire aerosol caused bronchospasm in some cases.

The inhalation of a mixture of 80 per cent helium and 20 per cent oxygen has often been recommended for asthma. Schiller and his coworkers,[242] however, found that it had no greater effect on the expiratory reserve volume, vital capacity, and oxygen saturation in the asthmatic patient than the breathing of air.

Physical therapy and respiratory exercises in the treatment of asthma were commended by May,[176] Livingstone,[165] Schlesinger,[243] Whitfield,[291] M. E. Miller,[185] Fein et al[92] and Barach.[17] May[176] pointed out that detailed instructions in the exercises and posture training are exacting and time consuming, but must be persisted in until the pattern becomes automatic to the patient. According to Livingstone,[165] 60 per cent of patients learned to abort minor attacks of asthma after three to nine weeks of training. While the results are difficult to assess because of the many variables, only 10 per cent failed to improve materially. After treatment with breathing exercises only, without medication or environmental changes, thirty-seven of forty-nine "allergic" asthmatics and fifteen of twenty-six "infective" asthmatics showed marked improvement.

Miller[185] of the Johns Hopkins Hospital modified the customary breathing exercises of the Asthma Research Council of London to emphasize expiration as the active phase of respiration, accomplished by contraction of the abdominal and external intercostal muscles, leaving inspiration as the passive phase. Detailed instructions are given in her article, but individual training of the patient is essential. Evaluation of the results is difficult, but improvement was noted in about 90 per cent of cases even when emphysema was present. The newly acquired mode of respiration can become automatic and habitual through practice, and can be employed to combat exertional dyspnea. While they observed no significant increases in vital capacity, Fein et al[92] found respiratory exercises to be a valuable supplementary measure in the treatment of asthma. The patient is taught to avail himself of the lower portion of the thorax as well as the upper and

to use the diaphragm to a greater than normal degree. Prolonged and close supervision, up to one year, is required. Once "controlled breathing" is mastered, the patient achieves a sense of security and the ability to abort mild attacks. Barach[17] stressed the value of breathing exercises in the geriatric age group with asthma and emphysema, including the learning of diaphragmatic breathing, manual compression of the lower thorax and abdomen, and the employment of the headdown position.

Faiez and Ragheb[90] noted a general improvement as regards the number, duration, and severity of asthmatic attacks after five to ten daily intravenous injections of 10 mg of desoxycorticosterone acetate and 1 gm of ascorbic acid. Female patients responded less well than male, and those at or past the menopause not at all.

Benmussa et al[26] reported effective relief from the subcutaneous implantation of amnion. Three fragments of amnion were placed beneath the abdominal skin on one to five occasions at eight or ten-day intervals. The results were excellent in eight cases, five of whom were considered "cured" for more than a year; good in one, fair in two, and poor in two cases. In three cases, the attacks ceased after the first implant. An increase in the dyspnea and expectoration after two or three days often occurred, but did not require interruption of the therapy. There were no reactions except slight local inflammation once, and no implants were lost.

A. Brown[40] claimed a 90 per cent "cure" rate from days or months of daily carbon dioxide inhalations through tubes in the nose for ten to thirty minutes. Complicating bronchitis, unresolved pneumonia, emphysema or cardiovascular disease led to less impressive improvement.

Santenoise et al[238] reported excellent results with a vagotonin-free preparation of centropneine, a hormone recently isolated from the pancreas, administered three times a day for two weeks to six months. Significant benefit was noted in 125 patients, of whom forty had complete relief from asthma. Treatment was unsuccessful in seventeen patients for several reasons.

ASTHMA IN CHILDREN

Collins-Williams and Ratner[58] reviewed the subject of pediatric asthma and other allergies. Logan[166] and Criep[61] indicated that the treatment of asthma in the child is essentially the same as in the adult. Rackemann[218] discussed the long-range care of allergic children, emphasizing symptomatic control, the prevention of infection, and the use of vaccines, which have a nonspecific beneficial effect provided local reactions are produced. In reviewing the ultimate outcome of pediatric asthma, he pointed out that not infrequently, following the disappearance of asthma in the patient's late teens or early twenties, the patient may be well for a number of years, only to acquire typical grass or ragweed hay fever or both at the age of thirty years or so. In commenting on the follow-up study of Rackemann and Edwards, which was reviewed last year,[114] an editorial[86] notes that the parents of an asthmatic child can be given the general facts concerning prognosis. However, such generalizations do not enable the physician to prognosticate about the individual child. It is helpful, nevertheless, to know that so many asthmatic children are free from symptoms twenty years later.

Buffum[48] studied the etiology of asthma in thirty private cases seen before the age of one year. The clinical sensitivities were determined by history and feeding tests plus scratch tests. In general, inhalant and food

allergens were found to be the causative factors, with respiratory infection as an additional element. Only one infant had a positive scratch test to house dust, but several seem clinically allergic to it, so it seems that clinical sensitivity antedates the skin reactivity. Six other cases gave no positive skin tests at all, but nevertheless seemed extrinsically allergic to house dust and foods. Many foods such as orange, wheat, and milk gave more positive clinical tests than scratch tests. At this age, orange and egg were the most frequent allergens, and milk and wheat were less common sensitizers but were more difficult to diagnose.

Ratner[222] was impressed with the fact that thyroid therapy of the allergic child is a rewarding experience. The usual measures for the diagnosis of hypothyroidism are obviously impractical as office procedures in the pediatric age group. He consequently resorted to an appraisal of thyroid hypofunction by means of bone maturation roentgenographic studies of the hands and wrists, and of capillary microscopy of nail folds. It is granted that retardation of epiphyseal development and abnormal capillary patterns may be caused by other factors than hypothyroidism. Thyroid medication is usually started with ¼ grain in the younger age group and ½ grain in the older child, subsequent dosage being controlled by clinical observation. It is seldom necessary to exceed two grains of desiccated thyroid daily. In respiratory allergies, thyroid therapy apparently aids in reducing mucosal edema in the respiratory tract. Asthmatic children in this group whose attacks are at times precipitated by strong winds and physical exertion, often respond to thyroid by no longer having such nonspecific episodes. In his experience, thyroid therapy did not relieve the true allergic attacks of asthma nor lessen their frequency. It did improve the endurance and general vigor of the child.

COMPLICATIONS

As every allergist knows, the sequelae of bronchial asthma are numerous and difficult to manage. This section will conclude with a consideration of other conditions occurring in asthmatic patients.

Cough Syncope.—Derbes and Kerr[72,154] called attention to the syndrome of after-cough fainting as a complication of asthma. First described by Charcot in 1876, it has been given a number of names, including post-tussive syncope, bronchial syncope, cough syndrome, tussigenic ictus, and the like. Other conditions produce the syndrome. Of forty cases, ten had asthma. Others had pulmonary emphysema and miscellaneous broncho-pulmonary disorders. It is estimated that 8 per cent of asthmatics present this syndrome. It is characterized by sudden syncope following a vigorous unproductive cough. The period of unconsciousness is brief and the patient promptly resumes his activities without fatigue or malaise. Occasionally, limited convulsions occur. Minor episodes may produce only giddiness and impaired vision. The syndrome is limited almost exclusively to males of middle age who are robust or obese, and who indulge heavily in smoking, drinking, and eating. The clinical course is variable, paralleling the underlying disease, and while usually benign, in rare instances results fatally. Injuries are sometimes sustained in falling. The mechanism of the syncope is unknown, but may depend on pulmonary vasospasm or a vagal reflex. Treatment is essentially symptomatic, including therapy of the asthma or other underlying disease, cocainization of sensitive areas, procaine block of the superior laryngeal nerve, weight reduction, and limitation of smoking and alcohol.

Bronchostenosis.—Benign nontuberculous bronchostenosis was found in 327 of 1,034 cases of intrinsic or extrinsic asthma bronchoscoped at the Mayo Clinic in a ten-year period, according to Mears, Prickman and Moersch.[181] While all age groups were represented, the greatest incidence occurred between thirty and fifty-nine years of age. The commonest symptom was cough, persistent or paroxysmal; fever was present in 59 per cent and hemoptysis in 35 per cent. Upper respiratory infections, pneumonia, and pleurisy occur frequently. Physical examination may disclose no abnormal findings other than asthmatic râles, but in 39 per cent of the series signs of obstructive pneumonitis were present. Roentgenograms were abnormal in only 30 per cent of the cases, and usually suggested atelectasis or, less often, bronchiectasis. Bronchoscopic examination was diagnostically definitive. The stenosis occurred much more often in the right lung than the left, and the superior division of the lower lobe was the most frequent site. In some cases, more than one stenosed bronchus was encountered. Needless to say, other conditions can cause bronchostenosis. Treatment consisted of dilatation of the stenosed bronchus and aspiration of the retained secretions. Prompt improvement occurrred in 60.5 per cent of cases. Recurrences are best prevented by the avoidance and prompt treatment of respiratory tract infections.

Turiaf, Rose and Marland[277] diagnosed irreversible stenoses of lobar and segmental bronchi by bronchography and bronchoscopy. They recognize two types: (1) stenosis from inflammatory swelling of the mucosa, and (2) stenosis from hypertrophy of the muscularis and elastica of the bronchi. More or less frequently superimposed on these are the paroxysmal factors of spasm and hypersecretion which enhance or complete the obstruction of the bronchial lumen.

Emphysema.—No more perplexing problem faces the allergist than the evaluation of and management of pulmonary emphysema. According to Whitfield,[291] the degree of emphysema can be more readily and more accurately determined by ordinary clinical assessment and by spirometry than by roentgenographic study. Fletcher[97a] showed clearly, however, that the clinical diagnosis cannot be made with any confidence, at least by a single observer, except perhaps in the most advanced cases. Eight highly experienced clinicians, separately examining twenty patients, expressed tremendous disagreement regarding the presence or absence of emphysema and of specific physical signs. There was similar discrepancy in assessing the dyspnea. It was concluded that there is little hope of the clinician's being able to diagnose the early stages of emphysema, and pulmonary function studies must be employed.

Geschickter and Popovici[108] found that postasthmatic pulmonary emphysema frequently caused some degree of arterial hypertension. Of seventy-five patients over forty years old who had had bronchial asthma for two or more years, sixty had emphysema. Of these, twenty-eight (46 per cent) had hypertension, usually in the range of 170 to 190 mm Hg systolic and 110 to 120 diastolic. Aside from asthma, concomitant pulmonary fibrosis, postural lordosis, and obesity occurring in association with emphysema increase the likelihood of hypertension. Postemphysematous hypertension appears to result from the loss of intrapleural negative pressure, leading to increased venous pressure in the inferior vena cava and so to renal congestion. Compensatory renal arteriolar spasm and generalized arteriolar spasm follow. Both the hypertension and the asthma may improve on

treatment with digitalis or coronary dilators. The incidence of myocardial infarction is also thought to be increased in postasthmatic emphysema. Of sixty cases, twenty-one had electrocardiographic evidence of myocardial damage.

The treatment of pulmonary emphysema has been considered by Segal and Dulfano[245,246] and Barach.[16] Those interested in this problem are referred to a series of publications by Barach and his coworkers.[18-22] Emphasis is placed on the use of "viscero-abdominal" breathing accomplished by the headdown position. Physical and mechanical methods are employed to simulate the mechanisms of human cough, utilizing such apparatus as the exsufflator and the mechanical cough chamber. Low abdominal belts and pneumoperitoneum have also been employed. Intermittent positive pressure breathing has been recommended by Smart et al[257] among others. However, Fowler and his coworkers[100] failed to confirm its value. They found that, judged by symptomatic improvement and by the results of various pulmonary function tests, aerosolized isopropyl arterenol was superior to oxygen administered by intermittent positive pressure breathing, and the results were no better when the aerosol was administered by means of the intermittent positive pressure apparatus.

Respiratory depression followed by delirium and coma may develop in patients with chronic pulmonary emphysema while receiving oxygen therapy. Segal et al[247] stated: "In general, there has been an overemphasis on the danger of inducing the carbon dioxide intoxication syndrome and respiratory acidosis by the sudden administration of high concentrations of oxygen in patients with classical, intractable bronchial asthma. This danger, however, is always present in patients with chronic hypoxia secondary to chronic pulmonary emphysema or chronic pulmonary heart disease, particularly if respiratory-depressing drugs are administered preceding or in conjunction with the high concentrations of oxygen."

Respiratory acidosis, from whatever cause, is basically due to ineffective alveolar ventilation, according to Segal and his colleagues.[248] Although a tentative diagnosis may be made from the clinical manifestations, definitive diagnosis is based on the carbon dioxide content and pH of arterial blood or venous blood drawn anaerobically. Whether the disturbance follows the acute relief of hypoxia by oxygen, followed by hypercapnia, or from depressed alveolar ventilation due to drugs, the syndrome manifests itself when the pH falls below the normal range. Other factors involved in the mental symptoms are the hypoxia itself, decreased cerebral oxygen consumption, and cerebral vasospasm. Mithoefer[189] demonstrated increased intracranial pressure as one of the factors. An editorial[81] considers the syndrome an example of "paradoxical therapeutics" and states that fortunately, it is not usually encountered in the course of the acute attack of bronchial asthma or in status asthmaticus unless the patient has underlying chronic pulmonary emphysema. An illustrative case was recently described.[52]

Schrire and Schrire[244] observed an instance of subcutaneous and mediastinal emphysema complicating status asthmaticus. Surgical decompression was necessary and was effective.

Cor pulmonale.—Samuelsson[237] investigated 363 cases of bronchial asthma, chronic bronchitis and pulmonary emphysema and found that 218 had electrocardiographic or roentgenographic evidence of cor pulmonale. The incidence was highest in the older patients. Clinical diagnosis is diffi-

cult, but the onset of dyspnea at rest in a patient with uncomplicated emphysema is the first clinical sign of decompensation. Nearly one-half of the patients had electrocardiographic abnormalities. These included right axis deviation; elevated P_2 and P_3; changes in T_2 and T_3; inversion of the T wave in parasternal leads; changes in ST_{II} and ST_{III}; right bundle branch block; or low voltage in the standard leads. X-ray abnormalities, present in one-third of the patients, included prominence of the pulmonary arch, right heart enlargement, or an increase in the width of the right or left pulmonary artery.

R. D. Miller et al[186] studied the relationship of arterial hypoxia to disability and to cor pulmonale in 240 patients with chronic pulmonary emphysema. Although the incidence of hypoxemia was greater in patients with more marked clinical disability, the presence or absence of hypoxemia did not govern the degree of disability in individual cases. Cor pulmonale with congestive failure, when present, occurred almost exclusively among patients who had either transient or persistent hypoxemia.

Harvey, Ferrer and Cournand[132] pointed out that the treatment of chronic cor pulmonale must include an attack on the pulmonary insufficiency as well as on the cardiac state. Among other measures, aerosols of Vaponefrin® or some similar preparation should be administered three or four times a day by either manual or positive pressure. Antibiotics should be used to control infection and even a trivial respiratory infection should not be ignored. Acute exacerbations of the cardiopulmonary insufficiency are most serious and require emergency therapy, including oxygen if the anoxic patient is not hypercapnic, or pressure breathing if he is. Cardiac therapy comprises digitalization, low-salt diet and, when necessary, mercurial diuretics. Morphine, codeine and the barbiturates are contraindicated, but chloral hydrate or paraldehyde may be given if sedation is absolutely necessary. Other measures include phlebotomy, steam inhalation, potassium iodide or terpin hydrate, and an adequate fluid intake. The problem of the heart failure can almost invariably be resolved, but the pulmonary insufficiency remains and is sometimes fatal. Similar measures have been outlined by others.[53]

Spontaneous Pneumothorax.—Russell and Macfarlane[232] described a case of fatal spontaneous pneumothorax occurring while the patient was hospitalized. Death ensued in two or three minutes. At necropsy the site of the pleural rupture could not be found. The rarity of this complication in asthma is emphasized.

Relationship of Asthma to Other Conditions.—A considerable incidence of *eczematous dermatoses* is seen in patients with asthma, according to Diamond.[74] Of 179 cases of respiratory allergy, 9.5 per cent had a concomitant atopic dermatitis. Of twenty-three patients with a primary complaint of atopic dermatitis, seven had respiratory symptoms caused by inhalant allergens. The dermatoses often improved coincidentally with the treatment of the respiratory allergy by hyposensitization with inhalant allergens. Exacerbations of dermatitis caused by inhalants sometimes occurred following overdosage with such extracts. Ratner et al[223] also commented on the allergic dermal respiratory syndrome in children.

Harkavy and Perlman[130] reviewed the subject of *vascular allergy* as a complication of prolonged or neglected asthma. Where the exciting agents are not determined and/or not eliminated by proper treatment early enough

in the course of the patient's illness, prolonged disease due to the persistence of the allergenic stimulation may ensue. Three categories are recognized: (1) bronchial asthma and/or cough with eosinophilic pulmonary infiltrations (Löffler type); (2) bronchial asthma with prolonged recurrent pulmonary eosinophilic infiltrations; and (3) bronchial asthma with recurrent pulmonary eosinophilia and hyperergic vascular reactions in the heart, serous membranes, kidneys and other organs. The reactions in the vessels may vary from simple arteritis to necrotizing arteritis, periarteritis nodosa or endarteritis obliterans.

Drug tolerance is reduced in asthmatics, according to Waldbott et al.[289] Although they maintained that the demise of a patient seven hours after an intravenous injection of sodium salicylate was a fatal intoxication from a "physiologic" dose rather than an anaphylatic shock, the implication is clear, and is confirmed by animal experiments, that care is required in administering drugs to the allergic patient.

Studies of the effect of *pregnancy* on asthma by Jensen[147] and Quarles van Ufford[206] gave rather contradictory results. The former reported that of sixty-one cases, 41 per cent improved during pregnancy, 44 per cent were worse, and 15 per cent showed no change in their asthmatic symptoms. The improvement, if any, occurred chiefly in the first three months of pregnancy, but in those patients whose asthma was aggravated, the change took place at various times in pregnancy. Of those who improved, the majority promptly relapsed after delivery. In multiparous women, the variations in the severity of the asthma followed the same pattern in each of their pregnancies. Jensen discussed the possible indications for therapeutic abortion, because of severe attacks during pregnancy and uncontrollable aggravation after parturition. None of the patients in this series of cases was treated with hyposensitization in order not to introduce other variables; however, Jensen has never seen abortion to result from hyposensitization.

In contrast, in the patients observed by Quarles van Ufford[206] the asthma fairly uniformly exacerbated during the first part of pregnancy, and subsequently tended to decline. Fifty patients reported the following fluctuations: 10 per cent became worse in the first three months of pregnancy and 2 per cent in the last six months; 36 per cent were free of symptoms during pregnancy; 4 per cent had symptoms only during pregnancy; and 90 per cent aggravated after delivery, including 6 per cent with asthma in the post-partum period only. The intensity of allergic skin tests decreased somewhat after the early months of pregnancy. Blood eosinophil counts showed no significant change during pregnancy but a transient increase frequently appeared in the puerperium. The Thorn test and 17-ketosteroid excretion varied during pregnancy, and tended toward decreased values after delivery. Other endocrine landmarks gave the following findings. Of 100 pubertal female asthmatics, eighteen were worse before the menarche, one was worse after it, and one had subsidence of symptoms postmenarche. In a larger series of adult female asthmatics, 15 per cent reported that their asthma started soon after the menarche. A similar group reported the following effect of menstruation on their asthma: 28 per cent were worse and none was better before, 4 per cent were worse and 2 per cent were better during, and 1 per cent was worse and 2 per cent were better after menstruation, and 2 per cent had asthma only during menstruation; 61 per cent were not affected in either way. In an older age group, 3 per cent were better, 85 per cent were

unaffected, and 2 per cent were worse during the climacteric, while 10 per cent started to have asthma only at the menopause.

Gutmann[120] found statistical evidence of an "antagonism" between *diabetes mellitus* and bronchial asthma. Only thirty-five of 19,126 patients with diabetes mellitus mentioned in the literature had asthma. Among 2,000 of his allergic patients only five were diabetics. One patient had both diseases, but in two patients the conditions alternated so that they were free of asthma when their blood sugar levels were above 150 mg per 100 ml. Four of twelve asthmatics treated with cortisone and corticotropin had glycosuria and hyperglycemia; all four had family histories of diabetes. Siegal and Herzstein[253] discovered only three asthmatics among a group of forty diabetics with high insulin requirements. The incidence of asthma (and of latent atopy as determined by skin tests) was no greater in patients with severe diabetes than in a control group. However, according to Blanton et al[31] asthmatic subjects have a somewhat higher incidence of diabetes than the general population.

The *thymus* was enlarged in five infants with asthma present practically from birth and starting after an upper respiratory infection, as reported by Quarles van Ufford.[205] All had a family history of asthma. Roentgen irradiation or autogenous vaccines were used in therapy.

In a series of 100 asthmatic children studied by Holmgren and Kraepelien,[139] *electroencephalographic abnormalities* of varying degree and type were present in thirty-six. These included slow dysrhythmia, most evident occipitally, in twenty-two; partly focal spikes or sharp waves in three; general wave-and-spike episodes in three; and pathologically slow basic rhythm (α activity) in nine cases. In contrast to the earlier reports of Chobot and Dees, the electroencephalographic abnormalities did not correlate with the duration of the disease, but bore some relationship to the severity of the asthma. In some cases, electroencephalographic changes observed during the asthmatic paroxysm subsided when it was over. There is no satisfactory explanation of the high incidence of abnormal tracings in asthmatic children, but it may be due to the fact that periods of hypoxia can cause transient or permanent disturbances in the brain cells, or that allergic vascular changes, such as vasoconstriction, perivascular infiltration or edema, can cause cerebral dysfunction.

Logan and Saker[167] found the incidence of allergic disorders in the personal and family histories of patients with *cancer* to be significantly increased. Bronchial asthma was present in 9 per cent of 113 cases of carcinoma of the cervix uteri, in 10 per cent of eighty-two cases with malignant conditions of other organs, and in 3 per cent of ninety-seven noncancerous control subjects. An allergic family history was noted in 48, 44, and 14 per cent of the three groups, respectively.

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News Items

AMERICAN FOUNDATION FOR ALLERGIC DISEASES

Pursuant to its announced policy, the American Foundation for Allergic Diseases has issued another pamphlet for dissemination, in addition to those already published, giving informational material on allergic diseases. The most recent publication is an eleven-page illustrated booklet entitled "Hay Fever. What to Do About It." It is available for distribution by physicians to their patients, and can be obtained from the American Foundation for Allergic Diseases at 525 Lexington Avenue, New York, for ten cents each. It is a very compact, authoritative article which every hay fever patient should read. It also contains a ragweed pollen index for the United States and adjacent areas.

Other pamphlets available for distribution by the Foundation are "Answers to Some Questions about Allergy and Allergic Diseases" and "Allergy, the Hidden Foe."

An Executive Committee meeting of the Foundation was held in New York on July 10, at which Dr. Horace Baldwin, presiding, presented a progress report, which included a summary of activities since the Houston meeting and plans for the next two months. A financial report to June 30, 1954, was also presented, as well as an estimate of the budget for July and August. Plans for the year beginning September 1, 1954, including local committees, chapters, and membership, were discussed, and nominations for laymen trustees were also presented.

There is every indication that the Foundation is now well established and will develop rapidly into a foundation which will supersede all other efforts for a united front for a large scale educational program of research, publicity, and scholarship.

SECOND INTERNATIONAL CONGRESS OF ALLERGOLOGY

Plans are well under way for the Second Congress of the International Association of Allergology, comprising twenty-eight countries, to be held at the Hotel Quintandinha in Rio de Janeiro, Brazil, November 6-12, inclusive, 1955. The Program Committee is arranging a program, with the approval of the Organizing Committee of the Brazilian Allergy Society, which includes Nobel Prize winners and other outstanding scientists as guests speakers. There will also be many plenary sessions at which papers of ten minutes' length can be presented. The International Business Machine system will be used to present the talks in three languages, English, French and Spanish.

The Brazilian Allergy Society, of which Dr. E. Brum Negreiros is President, and Dr. Ulysses Fabiano Alves, is Secretary-General, together with their committee, has assured us that, through the aid of the Brazilian Federal Government and the Government of the City of Rio de Janeiro, as well as through revenue from the technical and commercial exhibits, they will have adequate facilities for financing the local expenses.

Arrangements have been made through the Bankers and Merchants Travel Service, 511 Fifth Avenue, New York 17, N. Y., telephone, Murray Hill 7-6938, to publicize the meeting in North America by sending out a letter, with travel information, through the President of the Association, Dr. F. W. Wittich, with headquarters at 424 LaSalle Medical Building, Minneapolis, Minn. This travel information, prepared for ready reference, outlines the various ways and means of travel to and from Rio de Janeiro. In order to facilitate the travel arrangements for the delegation from the United States the travel agency is asking the various steamship and airlines to set aside a block of accommodations on convenient departures from New

York and Gulf ports. Further through air rates from western cities are being prepared and will be available to those from that area. Those who wish to deal directly with the Bankers and Merchants Travel Service should address them at the above New York address. This letter, mailed to allergists in this country, will also contain health and visa requirements for travel in South America and essential requirements for United States citizens when making application for passport. Make application for your passports and visas as early as possible. The Bankers and Merchants Travel Service has offered to arrange for the visas.

Make your reservations early as there is an attendance of at least 1,200 expected. There is every reason to expect a deduction from your income tax for those who attend and participate in the programs or discussions. Those with limited incomes can make arrangements with the Pan-American Airlines for a minimum down payment, and monthly payments of the balance until the trip is paid for.

The Brazilian Allergy Society is making elaborate arrangements for entertainment for the wives and other relatives of those attending. Plan on taking your 1955 vacation in November at Rio. Every scientist or physician interested is cordially invited to attend.

Those interested in attending the Congress who have not received the packet and letter of information which was sent to all allergists in America may obtain this by writing to 424 LaSalle Building, Minneapolis. A very encouraging list of applicants has already been received.

BY-LAW AMENDMENT: ARTICLE IV, SECTION 4

An important item of business appearing on the agenda at the 1954 Annual Meeting of the Board of Regents held on Sunday, April 4, last at the Roney Plaza Hotel in Miami Beach, had to do with certain changes proposed and recommended in the "Qualifications and Requirements" prescribed by our By-Laws for election to Fellowship.

Dr. Hyman Miller's Committee, consisting of himself as Chairman and Drs. Rucks, Halpin, Gillaspie and Ratner, had earlier given lengthy study to this matter and had submitted a written report which was read to the Board, paragraph by paragraph, in which certain revisions in and to Article IV, Section 4, of the By-Laws were recommended for adoption. This entire By-Law was discussed and considered in great detail, after which a resolution was adopted recommending that certain changes in the "Qualifications and Requirements" for Fellowship as now set up, be modified and amended in several respects, and that after the same are rewritten will constitute an amendment to the By-Law in question. The resolution also provided that before this amendment would become effective, it be submitted for final study and comparison, as to form and context, to Dr. Wittich, Secretary-Treasurer, and to Mr. Bauers, College Counsel. Dr. Wittich and Mr. Bauers have now completed their consideration and final draft of these provisions and have submitted the same to Dr. Hyman Miller, Chairman of the Committee, who has given his complete endorsement and approval thereto.

Under the resolution adopted by the Board of Regents, Article IV, Section 4, of the By-Laws is therefore amended to include the following provisions as to "Qualifications and Requirements."

Section 4. Election of Fellows

Unless otherwise fixed and determined by the Board of Regents, the membership of the College shall be unlimited. New Fellows may be admitted at any time.

Election of Active Fellows.

(a) Qualifications and Requirements:

1. He shall have qualified and served a minimum period of three years as

an Associate, except upon recommendation of the Board of Regents by reason of very special qualifications as hereinafter set forth.

2. He shall have been graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and if engaged in practice, his professional activity must be confined at least 50 per cent to the field of allergy.

3. If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of allergy at a permanent location for at least three years preceding nomination for Active Fellowship. The Board of Regents shall be given discretionary power to modify this ruling under exceptional conditions.

4. The criteria of eligibility for election to Active Fellowship are to be based on detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions in media acceptable to the Board of Regents, with particular emphasis upon papers published during the period of Associateship; personal approval by those listed as references on his application form, including his sponsor, with reference to his character, ethical standing and medical activities; evidence of postgraduate training, including the Instructional Course conducted by the College and attendance upon the Annual Meetings of the College.

(b) Proposal:

His name shall be proposed on the official blank of the College by an Active Fellow of the College, who may or may not be an officer, but who must be familiar with the applicant's character, including personal qualifications, professional ethics and attainments. His application must be accompanied by a list of his publications, membership in medical and honorary societies and whether certified by a specialty board. His recommendation must be accompanied by an adequate written statement made by those listed on his application blank as sponsor and references, containing all of the above cited qualifications of the candidate. The proposer must be prepared to add such further information as may be requested by the Board of Regents. If the applicant has been a member of the Air Force, Army, Navy or Public Health Service, he must be proposed by an Active Fellow accompanied by a recommendation by his superior medical officer, or in special instances, the sponsor may be an officer of the College or even a member of the Board of Regents.

(c) Election:

The credentials of the candidate shall be considered by the Board of Regents for election or rejection. Election shall require a two-thirds vote of the Board of Regents.

(d) Notification:

Successful candidates shall be so notified immediately after their election and shall be urged to attend the next succeeding Annual Meeting, when Active Fellowships will be formally conferred. The official Active Fellowship Certificate, signed by the President and the Secretary, shall be issued following the Annual Meeting.

(e) Exceptions:

1. Proposals for direct election to Active Fellowship, with or without prior certification by the appropriate certifying board, may be made to the Board of Regents. This manner of election is an unusual mark of distinction; hence such candidates must be pre-eminent in teaching, research or clinical practice. In advancing individuals for such consideration, the following additional details must be

considered: mature experience, national reputation, publications and other contributions to medical science and public welfare. The Board of Regents will exercise due discrimination in all proposals for direct election to Active Fellowship.

2. Proposals as in paragraph 1 above provided may not be invoked for candidates who have failed of regular advancement from Associateship to Fellowship.

WOMEN'S AUXILIARY

As Counsel for the College, I am happy to state that by the time this information appears in print and is read, the new Women's Auxiliary will have received its charter from the Secretary of State of the State of Minnesota. Mrs. Morris A. Kaplan, President, has been laboring with characteristic enthusiasm and energy to make the Auxiliary an actively functioning entity and to ensure its solid establishment. In her work, she has had the active and enthusiastic support and co-operation especially of Mrs. Boen Swinney, Treasurer, Mrs. J. Warrick Thomas, Secretary and Mrs. Homer E. Prince, as well as assistance from Mrs. Ethan Allan Brown, President-Elect, Mrs. Fred W. Wittich, Vice President, and Mrs. Lester L. Bartlett, Historian.

To give members of the College some idea of the character and scope of the activities of the Auxiliary, we are setting forth here some of the objects and purposes of the organization as the same will appear in its charter.

(a) To serve as an adjunct to The American College of Allergists by bringing its members into more active affiliation with organized medicine and particularly the specialty of allergy.

(b) To participate in and implement the activities of The American College of Allergists and assist in its efforts to extend medical knowledge and advance medical science; to assist in the preservation of public health; to enlighten and direct public opinion regarding the problems of physicians generally and those engaged in the practice of allergy; to foster and promote desirable public relations between those engaged in the science of medicine and the public; to participate in the conventions, activities, programs and meetings of The American College of Allergists.

(c) To initiate and conduct seminars, institutes, study groups and educational programs for the purpose of acquainting, educating and training its members in the science of medical economics, office management, personnel and patient contacts and other practical aspects of the business side of the practice of medicine which confronts the practicing allergists, one purpose thereof being to prepare and equip the members of the Auxiliary to give sound counsel, aid and assistance to members in the handling of such matters which so often prove of direct and intimate financial concern to them.

(d) To cultivate and promote cordial relations and mutual understanding among its members.

(e) To establish scholarships and assist in other work and activities, including fund raising activities, sponsored or approved by The American College of Allergists.

The corporation, under the corporate statutes of Minnesota, will possess all of the rights, privileges and immunities, and enjoy all the benefits applicable to corporations conducted not for profit.

There are to be three classes of membership, *active, associate* and *honorary*. The wives or widows of Active and Associate Fellows of the College, in good standing, will be eligible for Active membership, while the wives or widows of Honorary and Sustaining members, in good standing, will be eligible for Associate membership. Honorary memberships may also be conferred upon the unanimous recommendation of the Board of Governors, but only by reason of exceptional or meritorious service in the Auxiliary. The privilege of voting and holding elective office, however, will be restricted to Active members in good standing.

The general management of the business and affairs of the new Auxiliary is to be vested in a Board of Governors which will consist of ten members, nine of whom are to be elected from and by the voting members. Three of the first Board of Governors will serve for a one-year term, three for a two-year term, and three

for a three-year term. Commencing in 1955, and annually thereafter, three new members of the Board of Governors will be elected to serve for three-year terms. The President shall always be the tenth member of the Board of Governors. The following Active members will constitute the first Board of Governors:

Mrs. Homer E. Prince.....Houston, Texas
Three (3) year term expiring 1957
Mrs. Lawrence Halpin.....Cedar Rapids, Iowa
Three (3) year term expiring 1957
Mrs. Lester L. Bartlett.....Pittsburgh, Pennsylvania
Three (3) year term expiring 1957
Mrs. L. O. Dutton.....El Paso, Texas
Two (2) year term expiring 1956
Mrs. Orval R. Withers.....Kansas City, Missouri
Two (2) year term expiring 1956
Mrs. David Thomas, Jr.....Augusta, Georgia
Two (2) year term expiring 1956
Mrs. M. Murray Peshkin..... New York City, N. Y.
One (1) year term expiring 1955
Mrs. Leon Unger.....Chicago, Illinois
One (1) year term expiring 1955
Mrs. Johnny A. Blue.....Oklahoma City, Oklahoma
One (1) year term expiring 1955
Mrs. Morris A. Kaplan, President.....Chicago, Illinois

The first annual meeting of the Auxiliary will be held at the Morrison Hotel in Chicago at the same time The American College of Allergists holds its annual meeting there in 1955. At that time, a complete set of By-laws, now in preparation under the supervision and direction of the President, will be read and presented by her to the membership for adoption. Many other important matters of business will also appear on the agenda of that meeting.

ELOI BAUERS

* * *

Although she passed away on April 24, 1954, the name of Mrs. Alexander R. Altose of Seattle will be entered on the charter membership list of the newly-formed Women's Auxiliary. Dr. Altose, himself a charter member of the College, felt this would be a fitting tribute to her memory.

MICHIGAN ALLERGY SOCIETY

At the annual meeting of the Michigan Allergy Society, the following officers were elected:

President.....Joseph H. Shaffer, M.D., Detroit
Vice President.....Sidney Friedlaender, M.D., Detroit
Secretary-Treasurer.....Kenneth Mathews, M.D., Ann Arbor

NEWS OF COLLEGE MEMBERS

Dr. Granville S. Knight, F.A.C.A., Santa Barbara, California, was elected president for 1954-55 of the American Nutrition Society.

Dr. William Kaufman, 540 Brooklawn Avenue, Bridgeport, Connecticut, an Active Fellow in the College, read a paper on "Transference in the Psychotherapy of Patients with Food Allergies" at the International Congress for Psychotherapy in Zurich, Switzerland, in July.

BOOK REVIEWS

PSYCHOSOMATIC CASE BOOK. By Roy R. Grinker, M.D., Director, Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, Clinical Professor of Psychiatry, University of Illinois College of Medicine, and Fred P. Robbins, M.D., Associate Psychiatrist, Michael Reese Hospital and Staff Member, The Chicago Institute for Psychoanalysis. 346 pages. Price, $6.50. New York: The Blakiston Co., Inc., 1954.

The purpose of this text book is to introduce the student to the basic principles of a psychosomatic approach in medicine. Seventy-nine clinical histories of patients are grouped into three sections for purposes of illustrating general concepts—problems of diagnosis, special syndromes, and therapeutic methods. Representative syndromes have been chosen to illustrate the common affections of various systems; some are presented at considerable length, others more briefly. The language and the form of presentation should lend themselves to the ready understanding of students at various levels of those professions dealing with the sick.

A bibliography and index are included. —I.W.

PHYSIOLOGICAL METHODS IN CLINICAL PRACTICE. By William S. Middleton, M.D., Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin. American Lecture Series. 40 pages. Springfield: Charles C Thomas, 1954. Price $1.00.

This small monograph contains The Beaumont Lecture of the Wayne County Medical Society, Detroit, Michigan, February 2, 1953. Over one hundred and thirty years ago the young Army surgeon, William Beaumont, attended a young French-Canadian who had been wounded by a charge of powder and duck shot, which entered the thorax posteriorly and traversed the lower left chest and diaphragm to penetrate the stomach and emerge anteriorly. A thoraco-abdominal wound would be considered most dangerous traumata even under prevailing advantages of modern surgery and medicine. For more than two years Beaumont administered meticulous medical care to his patient, and in addition furnished him lodging and board from his limited income as a very junior Army surgeon. Beaumont made 238 observations on the physiology of the intact human stomach between May, 1825, and November, 1833, under difficult circumstances and with a meager background for physiologic investigation, never having attended a medical school. Beaumont's description of the gastric juice is classical: ". . . is powerfully antiseptic, checking the putrefaction of meat; and effectually restorative of healthy action, when applied to old, foetid sores, and foul, ulcerating surfaces." This last statement has unusual historical significance, although there was no early acceptance nor wide application of Beaumont's therapeutic intimation. J. Henri Fabre, the French naturalist, later suggested a proteolytic action of the greenbottle grubs in preparing protein foods for assimilation. The cleanliness of wounds infested with maggots, during World War I, led to their purposeful introduction for the treatment of infected wounds. This biological approach was analogous to Beaumont's observations on the gastric juice. With improved antisepsis, sulfonamides and antimicrobial agents this method of therapy has been relegated to limbo, but a renewed interest in the biologic resolution of products of inflammation may be noted in the application of streptodornase, streptokinase and trypsin in this relation.

This book should have an appeal for all those interested in the historical background of medicine.—*M.M.*

A MANUAL OF TROPICAL MEDICINE. Second Edition. By Thomas T. Mackie, M.D., Colonel, M.C., A.U.S. (Retired); George W. Hunter, III, Ph.D., Colonel, M.S.C., U.S.A.; C Brooke Worth, M.D. 907 pages, including index, 304 illustrations. Price, $12.00. Philadelphia, W. B. Saunders Company, 1954.

The first edition of this Manual of Tropical Medicine was published during World War II, one of a group of studies prepared to meet the needs of the Armed Forces in the tropics. The revolutionary situations, the growth of Nationalism, and the wealth of raw materials existing in the backward, undeveloped regions of this world have all tended to heighten the importance of these areas. These factors, together with the augmented responsibilities of public health workers to control preventable endemic and communicable diseases, have stimulated research and, as a result, rendered much of the first edition of the book obsolete. Several sections have been rewritten and material in others deleted.

The contents of this volume are divided into twelve sections: Virus Diseases, Rickettsial Diseases, Spirochetal Diseases, Bacterial Diseases, Mycotic Diseases, Protozoal Diseases, Helminthic Diseases, Nutritional Diseases, Miscellaneous Conditions, Medically Important Molluscs, Medically Important Arthropods, and Some Laboratory Diagnostic Methods.

The shift in emphasis on some diseases and the authors' field experience have led to the inclusion or substitution of new chapters on the virus encephalitides, trachoma, rickettsialpox, trench fever, leptospiral diseases, leprosy, toxoplasmosis, gnathostomiasis, trichostrongyliasis, the nutritional diseases, effects of heat, epidemic hemorrhagic fever, and medically important molluscs. Other chapters, extensively revised, are those dealing with the rickettsial diseases, relapsing fever, the dysenteries, malaria, schistosomiasis, filariasis, and laboratory techniques. It might also be indicated at this point that the diseases dealt with in this volume are not restricted to the tropics and subtropics.

Materials in this book have been drawn from many sources. The manual is amply illustrated, and the index appears to be a satisfactory one.—I.W.

THE DYNAMICS OF VIRUS AND RICKETTSIAL INFECTIONS. International Symposium sponsored by The Henry Ford Hospital. Edited by Frank W. Hartman, M.D., Frank L. Horsfall, Jr., M.D., and John G. Kidd, M.D., Detroit, Michigan. 461 pages. New York: The Blakiston Company, Inc., 1954. Price $7.50.

This volume constitutes the proceedings of the International Symposium on the Dynamics of Virus and Rickettsial Infections held in Detroit, Michigan, October 21, 22, and 23, 1953, under the auspices of the Henry Ford Hospital. One of the primary objectives of the symposium was to provide opportunity for exchange of ideas and information between workers in the various fields of virus and rickettsial diseases. Five major subjects were discussed: Mechanisms of virus and rickettsial infections, ecology and pathogenesis of virus and rickettsial infections, laboratory diagnosis of virus and rickettsial infections, and approaches to prophylaxis and therapy of virus and rickettsial infections. Thirty-three outstanding investigators in this field, many from distant parts of the world, participated in the symposium. Dr. J. Ralph Audy came from Malaya, Mr. F. C. Bawden, Dr. A. W. Downie and Dr. F. O. MacCallum came from England, Dr. Alfred Gottschalk from Australia, and Dr. Preben von Magnus from Denmark. Other eminent workers came from twenty-one institutions located in various parts of the United States. Over four hundred scientists attended the symposium, in addition to those who gave papers, and many of these participated in the discussions. The field of virus and rickettsial infections has theoretical interest for scientists. A review of current knowledge in this field should have wide usefulness since information on virus and rickettsial infections has theoretical interest for scientists in a number of disciplines, and also

importance for practicing physicians. The amount of new information which is emerging, and the concepts which are rapidly developing in the study of these infectious agents, provide added reasons for survey of the ideas and findings of a large group of prominent workers, and this symposium affords this opportunity.—*M.M.*

DIZZINESS. An Evaluation and Classification. By David Downs DeWeese, M.D., Clinical Professor of Otolaryngology, University of Oregon Medical School, Portland, Oregon. Edited by Roscoe L. Pullen, M.D. 80 pages. Springfield: Charles C Thomas. American Lecture Series, 1954. Price $2.75.

This monograph represents the author's thesis for membership in the American Laryngological, Rhinological and Otological Society, and is an attempt to clarify the confusion which exists regarding dizziness. Enlargement of the author's study has led to the present classification. The chapters include an introduction, anatomy and physiology of the Statokinetic system, nystagmus, definition of dizziness, and classification of dizziness which divides the symptoms as follows: nonsystematized dizziness which includes the eyes, proprioceptive system, and the central nervous system; systematized vertigo which includes the end-organ, the eighth nerve, the nuclei or brain stem. Chapter six is an evaluation of dizziness, Chapter seven outlines differential diagnosis of dizziness and the Eighth Chapter gives a summary and conclusions. The final chapter is devoted to report of cases and includes seventeen case histories. References and an index are included. This little monograph should be of use not only to the otologist but to the practitioner in other fields of medicine. —*M.M.*

DERMATOLOGIC MEDICATIONS. Marguerite Rush Lerner, M.D., Resident, Department of Dermatology, University of Oregon Medical School, and Aaron Bunsen Lerner, M.D., Associate Professor of Dermatology, University of Oregon Medical School, Portland, Oregon. 183 pages. Buckra cover. Chicago: The Year Book Publishers, Inc., 1954. Price, $3.50.

This timely new manual is a handy reference for simple and effective treatment of dermatologic conditions. It is divided into two sections: Therapeutic Agents and Treatment Regimens.

In the first section the commonly used agents found to be of greatest therapeutic value are listed, together with their chemistry, biochemistory and pharmacology, and are described under the following headings: Indication, Mode of Action, Dose or Application, and Side Effects. Adjuncts and cautions are listed in some instances. These therapeutic agents include anhidrotics; antihistamines and agents to combat sensitivity and acute tissue reactions; antipruritic lotions; liniments and ointments; chemotherapeutic agents; cleansers and baths; covermark; depigmenting agent; enzymic debridement; fungicidal and fungistatic agents; gelatin for finger-nails; heat rash agents; heavy metal antagonists; hyperpigmenting agents; insecticides and insect repellents; ion exchange resins; nitrogen mustard therapy; ointment bases and lubricating agents; protective agents against water, oils, organic solvents and sunlight; rosacea preparations; scalp preparations; seborrheic dermatitis preparations; sedatives and hypnotics; tar preparations; ultraviolet light; vitamins; wart removers, keratolytics and caustics; and wet dressings.

The second part outline regimens for disorders which require simultaneous and continuous treatment, such as acne vulgaris, eczematous dermatitis, chronic atopic dermatitis and lichen simplex, psoriasis, lupus erythematosus, and stasis ulcer. An easily followed elimination diet is given for cases suspected of food allergy. The punch biopsy procedure is described in detail.

This compact handbook should be of great help to all who treat skin disorders. It

is a handy working guide to 167 commonly used therapeutic agents found to be of greatest clinical value in everyday practice, and it contains the latest improved methods of specific treatment for the commonly encountered skin disorders of both children and adults.

—V.S.

AN Rh-Hr SYLLABUS. The Types and Their Applications. By Alexander S. Wiener, M.D., New York, N. Y. 82 pages. New York: Grune & Stratton, 1954. Price, $3.75.

This booklet in the Modern Medical Monograph series attempts to present an up-to-date summary of a complex subject in a concise, readable form. The information is uniquely presented in the form of a glossary, but is so arranged that the book is very easy to read from beginning to end.

Although the booklet, including index, covers only eighty-two pages, it deals with all facets of Rh-Hr types and with their applications in clinical and legal medicine and anthropology. In addition to chapters on fundamentals and Rh antibodies, it presents the serology and genetics of Rh-Hr types and directions for performing Rh antibody tests and titrations by several methods. Chapters on erythroblastosis fetalis, blood transfusions, and autosensitization are also included.

This volume is an introduction to the author's more advanced works, "Blood Groups and Transfusion," and "The Rh-Hr Blood Types; Applications in Clinical and Legal Medicine and Anthropology." This monograph contains all the necessary information on Rh-Hr types for readers who are not specializing in the field, and it will enable them to read and understand current literature on the subject.

Twenty tables and an index are included. —V.E.S.

GENERAL VIROLOGY. By S. E. Luria, Professor of Bacteriology, University of Illinois, Urbana, Illinois. 427 pages. New York: John Wiley & Sons, Inc., 1953. Price $8.50.

This book represents a new type of course in virology, presented by the author as a biological science to graduate and undergraduate students, first at Indiana University and more recently at the University of Illinois. It is an attempt to fulfill the need for a textbook in general virology. No details of actual techniques are given, but background information from the logarithms to the embryology of the chick embryo is covered. There are nineteen chapters which include an introduction to the science of virology, detection and identification of viruses, titration of viruses, size and morphology of virus particles, purification and chemical composition of virus material, serological properties of viruses, environmental effects on virus particles, virus-host interaction—the bacteriophage-bacterium system, the interaction of plant viruses with their host plants, the interaction of animal viruses with their hosts-tissue cultures—intracellular inclusions, growth of viruses in the chick embryo, hemagglutination phenomena and virus growth with summary on virus reproduction, interference phenomena in virus infections, variation in viruses with host variation and susceptibility to viruses, transmission, vectors, and survival of viruses, viruses and tumors, origin and nature of viruses, with an appendix on rickettsiae. There are 697 references in the bibliography-author index, as well as a complete index of the book itself. Virology is a rapidly developing science and original work is proceeding at such a pace that interpretations must often be revised before the final printing. However, virology has arrived at the stage where there is justification for an attempt at least at provisional integration. This book should contribute to such an integration.

—M.M.

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